STIC-ILL

From: Holleran, Anne
Sent: Wednesday, May 02, 2001 5:27 PM
To: STIC-ILL
Subject: refs. for 09/230,111

Examiner: Anne Holleran
Art Unit: 1642; Rm 8E03
Phone: 308-8892
Date needed by: ASAP

Please send me copies of the following :

1. Yangisawa, J. et al. J. Biol. Chem. (1997) 272(13): 8539-8545
2. Cuppen, E. et al. J. Biol. Chem. (1997) 272(48): 30215-30220
3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
4. Shieh, B.H. et al. Proc. Natl. Acad. Sci, U.S.A. (1997) 94(123): 12682-12687
5. Ranaganathan, R. et al. Current Biology (1997) 7(12): R770-R773
6. Montell, C. et al. Molecular Pharmacology (1997) 52(5): 755-763
7. Tsunoda, S. et al. Nature (1997) 388(6639): 243-249
8. Huber, A. et al. EMBO J. (1996) 15(24): 7036-7045

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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
4. Shieh, B.H. et al. Proc. Natl. Acad. Sci, U.S.A. (1997) 94(123): 12682-12687
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7. Tsunoda, S. et al. Nature (1997) 388(6639): 243-249
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3

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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
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4

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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
4. Shieh, B.H. et al. Proc. Natl. Acad. Sci, U.S.A. (1997) 94(123): 12682-12687
5. Ranaganathan, R. et al. Current Biology (1997) 7(12): R770-R773
6. Montell, C. et al. Molecular Pharmacology (1997) 52(5): 755-763
7. Tsunoda, S. et al. Nature (1997) 388(6639): 243-249
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5

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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
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5. Ranaganathan, R. et al. Current Biology (1997) 7(12): R770-R773
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8. Huber, A. et al. EMBO J. (1996) 15(24): 7036-7045

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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
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3. Sara, J. et al. J. Biol.Chem. (1997) 272(34): 20979-20981
4. Shieh, B.H. et al. Proc. Natl. Acad. Sci, U.S.A. (1997) 94(123): 12682-12687
5. Ranaganathan, R. et al. Current Biology (1997) 7(12): R770-R773
6. Montell, C. et al. Molecular Pharmacology (1997) 52(5): 755-763
7. Tsunoda, S. et al. Nature (1997) 388(6639): 243-249
8. Huber, A. et al. EMBO J. (1996) 15(24): 7036-7045

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(FILE 'HOME' ENTERED AT 15:52:30 ON 02 MAY 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:53:58 ON 02 MAY 2001

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L1            0 S SLGI
L2       599278 S FAS OR CD4 OR P75 OR SEROTONIN OR PROTEIN KINASE C OR ADENOMA
L3       269941 S SIGNAL TRANSDUCTION
L4       454795 S DOMAIN
L5      2300288 S INTERACT?
L6         1109 S L2 AND L3 AND L4 AND L5
L7       700029 S SCREEN?
L8           78 S L6 AND L7
L9           34 DUP REM L8 (44 DUPLICATES REMOVED)
L10        2350 S PDZ OR GLGF
L11           0 S L1 AND L3 AND L10
L12          71 S L2 AND L3 AND L10
L13          37 DUP REM L12 (34 DUPLICATES REMOVED)
```

L13 ANSWER 1 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2001130597 EMBASE
TITLE: Mitogen-stimulated TIS21 protein interacts with a ***protein*** - ***kinase*** - ***C*** .alpha.-binding protein rPICK1.
AUTHOR: Lin W.-J.; Chang Y.-F.; Wang W.-L.; Huang C.-Y.F.
CORPORATE SOURCE: W.-J. Lin, Inst. of Biopharmaceutical Science, National Yang-Ming University, Taipei, 112, Taiwan,Province of China. wjlin@ym.edu.tw
SOURCE: Biochemical Journal, (15 Mar 2001) 354/3 (635-643).
Refs: 33
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB TIS21 is induced transiently by PMA and a number of extracellular stimuli. Yeast two-hybrid screening has identified three TIS21 interacting clones from a rat cDNA library [Lin, Gary, Yang, Clarke and Herschman (1996) J. Biol. Chem 271, 15034-15044]. The amino acid sequence deduced from clone 5A shows 96.9% identity with the murine PICK1, a ***protein*** ***kinase*** ***C*** .alpha. (PKC.alpha.)-binding protein postulated to act as an intracellular receptor for PKC. A fusion protein of glutathione S-transferase and rPICK1 associates with the TIS21 translated in vitro, suggesting a direct physical interaction between these two proteins. TIS21 and rPICK1 are co-immunoprecipitated from NIH 3T3 cells overexpressing these two proteins. This indicates that the interaction also occurs in mammalian cells. Deletion of the ***PDZ*** domain at the N-terminus of rPICK1 abolishes its interaction with TIS21. A putative carboxylate-binding loop required for PICK1 to bind PKC.alpha. [Staudinger, Lu and Olson (1997) J. Biol. Chem 272, 32019-32024] is within this deleted region. Our results suggest a potential competition between TIS21 and PKC for binding to PICK1. We show that recombinant TIS21 is phosphorylated by PKC in vitro. The catalytic activity of PKC towards TIS21 is significantly decreased in the presence of rPICK1, whereas phosphorylation of histone by PKC is not affected, rPICK1 seems to modulate the phosphorylation of TIS21 through specific interactions between these two proteins. TIS21 might have a role in PKC-mediated extracellular ***signal*** ***transduction*** through its interaction with rPICK1.

L13 ANSWER 2 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2001:90891 BIOSIS
DOCUMENT NUMBER: PREV200100090891
TITLE: Independent anchoring and assembly mechanisms of INAD signaling complexes in Drosophila photoreceptors.
AUTHOR(S): Tsunoda, Susan (1); Sun, Yumei; Suzuki, Emiko; Zuker, Charles
CORPORATE SOURCE: (1) Departments of Biology and Neurosciences, Howard Hughes Medical Institute, University of California at San Diego,

La Jolla, CA, 92093-0649: susan@flyeye.ucsd.edu USA
SOURCE: Journal of Neuroscience, (January 1, 2001) Vol. 21, No. 1, pp. 150-158. print.
ISSN: 0270-6474.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In Drosophila photoreceptors the multivalent ***PDZ*** protein INAD organizes the phototransduction cascade into a macromolecular signaling complex containing the effector PLC, the light-activated TRP channels, and a regulatory PKC. Previously, we showed that the subcellular localization of INAD signaling complexes is critical for signaling. Now we have examined how INAD complexes are anchored and assembled in photoreceptor cells. We find that trp mutants, or transgenic flies expressing inaD alleles that disrupt the interaction between INAD and TRP, cause the mislocalization of the entire transduction complex. The INAD-TRP interaction is not required for targeting but rather for anchoring of complexes, because INAD and TRP can be targeted independently of each other. We also show that, in addition to its scaffold role, INAD functions to preassemble transduction complexes. Preassembly of signaling complexes helps to ensure that transduction complexes with the appropriate composition end up in the proper location. This may be a general mechanism used by cells to target different signaling machinery to the pertinent subcellular location.

L13 ANSWER 3 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001127823 EMBASE

TITLE: Human homologues of the Caenorhabditis elegans cell polarity protein PAR6 as an adaptor that links the small GTPases Rac and Cdc42 to atypical ***protein*** ***kinase*** ***C*** .

AUTHOR: Noda Y.; Takeya R.; Ohno S.; Naito S.; Ito T.; Sumimoto H.
CORPORATE SOURCE: H. Sumimoto, Dept. of Molecular/Structural Biol., Kyushu Univ. Graduate Sch. Med. Sci., Fukuoka 812-8582, Japan. hsumi@mailserver.med.kyushu-u.ac.jp

SOURCE: Genes to Cells,. (2001) 6/2 (107-119).
Refs: 43
ISSN: 1356-9597 CODEN: GECEFL
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background: Asymmetric cell division in the Caenorhabditis elegans embryos requires products of par (partitioning defective) genes 1-6 and atypical ***protein*** ***kinase*** ***C*** (aPKC), whereas Cdc42 and Rac, members of the Rho family GTPases, play an essential role in cell polarity establishment in yeast and mammalian cells. However, little is known about a link between PAR proteins and the GTPases in cell polarization. Results: Here we have cloned cDNAs for three human homologues of PAR6, designated PAR6.alpha., .beta. and .gamma., comprising 345, 372 and 376 amino acids, respectively. The PAR6 proteins harbour a ***PDZ*** domain and a CRIB-like motif, and directly interact with GTP-bound Rac and Cdc42 via this motif and with the aPKC isoforms PKC.iota./.lambda. and PKC.zeta. via the N-terminal head-to-head association. These interactions are not mutually exclusive, thereby allowing the PAR6 proteins to form a ternary complex with the GTPases and aPKC, both in vitro and in vivo. When PAR6 and aPKC are expressed with a constitutively active form of Rac in HeLa or COS-7 cells, these proteins co-localize to membrane ruffles, which are known to occur at the leading edge of polarized cells during cell movement. Conclusion: Human PAR6 homologues most likely play an important role in the cell polarization of mammalian cells, by functioning as an adaptor protein that links activated Rac and Cdc42 to aPKC signalling.

L13 ANSWER 4 OF 37 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:569570 CAPLUS
DOCUMENT NUMBER: 133:218040

TITLE: Deletion of the ***serotonin*** 5-HT2C receptor ***PDZ*** recognition motif prevents receptor phosphorylation and delays resensitization of receptor responses

AUTHOR(S): Backstrom, Jon R.; Price, Raymond D.; Reasoner, Darcie T.; Sanders-Bush, Elaine

CORPORATE SOURCE: Department of Pharmacology and the Center for Molecular Neuroscience, Vanderbilt University School of Medicine, Nashville, TN, 37232-6600, USA

SOURCE: J. Biol. Chem. (2000), 275(31), 23620-23626
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Phosphorylation-deficient ***serotonin*** 5-HT2C receptors were generated to det. whether phosphorylation promotes desensitization of receptor responses. Phosphorylation of mutant 5-HT2C receptors that lack the C-terminal ***PDZ*** recognition motif (Ser458-Ser-Val-COOH; .DELTA. ***PDZ***) was not detectable based on a band-shift phosphorylation assay and incorporation of 32P. Treatment of cells stably expressing .DELTA. ***PDZ*** or wild-type 5-HT2C receptors with ***serotonin*** produced identical maximal responses and EC50 values for eliciting [3H]-inositol phosphate formation. In calcium imaging studies, treatment of cells expressing .DELTA. ***PDZ*** or wild-type 5-HT2C receptors with 100 nM ***serotonin*** elicited initial maximal responses and decay rates that were indistinguishable. However, a second application of ***serotonin*** 2.5 min after washout caused maximal responses that were .apprx.5-fold lower with .DELTA. ***PDZ*** receptors relative to wild-type 5-HT2C receptors. After 10 min, responses of .DELTA. ***PDZ*** receptors recovered to wild-type 5-HT2C receptor levels. Receptors with single mutations at Ser458 (S458A) or Ser459 (S459A) decreased ***serotonin*** -mediated phosphorylation to 50% of wild-type receptor levels. Furthermore, subsequent calcium responses of S459A receptors were diminished relative to S458A and wild-type receptors. These results establish that desensitization occurs in the absence of 5-HT2C receptor phosphorylation and suggest that receptor phosphorylation at Ser459 enhances resensitization of 5-HT2C receptor responses.

REFERENCE COUNT: 27

REFERENCE(S):
(1) Akiyoshi, J; J Neurochem 1995, V64, P2473 CAPLUS
(2) Alblas, J; J Biol Chem 1995, V270, P8944 CAPLUS
(3) Backstrom, J; J Neurosci Methods 1997, V77, P109 CAPLUS
(4) Backstrom, J; Mol Brain Res 1995, V33, P311 CAPLUS
(5) Barker, E; J Biol Chem 1994, V269, P11687 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3

ACCESSION NUMBER: 2000123647 EMBASE

TITLE: ***PDZ*** -dependent activation of nitric-oxide synthases by the ***serotonin*** 2B receptor.

AUTHOR: Manivet P.; Mouillet-Richard S.; Callebert J.; Nebigil C.G.; Maroteaux L.; Hosoda S.; Kellermann O.; Launay J.-M.

CORPORATE SOURCE: J.-M. Launay, Service de Biochimie, Hopital Lariboisiere AP-HP, 2 rue Ambroise Pare, 75010 Paris, France. jean-marie.launay@lrb.ap-hop.paris.fr

SOURCE: Journal of Biological Chemistry, (31 Mar 2000) 275/13 (9324-9331).
Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Taking advantage of three cellular systems, we established that 5-HT(2B) receptors are coupled with NO signaling pathways. In the 1C11 serotonergic cell line and Mastomys natalensis carcinoid cells, which naturally express the 5-HT(2B) receptor, as well as in transfected LMTK- fibroblasts, stimulation of the 5-HT(2B) receptor triggers intracellular cGMP production through dual activation of constitutive nitric-oxide synthase (cNOS) and inducible NOS (iNOS). The group I ***PDZ*** motif at the C terminus of the 5-HT(2B) receptor is required for recruitment of the cNOS and iNOS transduction pathways. Indeed, the 5-HT(2B) receptor-mediated NO coupling is abolished not only upon introduction of a competitor C-terminal 5-HT(2B) peptide in the three cell types but also in LMTK- fibroblasts expressing a receptor C- terminally truncated or harboring a

point mutation within the ***PDZ*** domain. The occurrence of a direct functional coupling between the receptor and cNOS activity is supported by highly significant correlations between the binding constants of drugs on the receptor and their effects on cNOS activity. The 5- HT(2B)/iNOS coupling mechanisms appear more complex because neutralization of endogenous G.alpha.13 by specific antibodies cancels the cellular iNOS response while not interfering with cNOS activities. These findings may shed light on physiological links between the 5-HT(2B) receptor and NO and constitute the first demonstration that ***PDZ*** interactions participate in downstream transductional pathways of a G protein-coupled receptor.

L13 ANSWER 6 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:722032 CAPLUS
DOCUMENT NUMBER: 133:317686
TITLE: PICK1 interacts with and regulates PKC phosphorylation of mGLUR7
AUTHOR(S): Dev, Kumlesh K.; Nakajima, Yoshiaki; Kitano, Jun; Braithwaite, Steven P.; Henley, Jeremy M.; Nakanishi, Shigetada
CORPORATE SOURCE: Department of Biological Sciences, Faculty of Medicine, Kyoto University, Kyoto, 606-8501, Japan
SOURCE: J. Neurosci. (2000), 20(19), 7252-7257
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The G-protein-coupled metabotropic glutamate receptor sub-type 7a (mGluR7a) is a member of group III metabotropic glutamate receptors that plays an important role as a presynaptic receptor in regulating transmitter release at glutamatergic synapses. Here the authors report that the protein interacting with C-kinase (PICK1) binds to the C terminus (ct) of mGluR7a. In the yeast two-hybrid system, the extreme ct of mGluR7a was shown to interact with the PSD-95/Disks large/ZO-1 (***PDZ***) domain of PICK1. Pull-down assays indicated that PICK1 was retained by a glutathione S-transferase fusion of ct-mGluR7a. Furthermore, recombinant and native PICK1/mGluR7a complexes were coimmunopptd. from COS-7 cells and rat brain tissue, resp. Confocal microscopy showed that both PICK1 and mGluR7a displayed synaptic colocalization in cultured hippocampal neurons. PICK1 has previously been shown to bind ***protein*** ***kinase*** ***C*** .alpha.-subunit (PKC.alpha.), and mGluR7a is known to be phosphorylated by PKC. The authors show a relationship between these three proteins using recombinant PICK1, mGluR7, and PKC.alpha., where they were co-immunopptd. as a complex from COS-7 cells. In addn., PICK1 caused a redn. in PKC.alpha.-evoked phosphorylation of mGluR7a in in vitro phosphorylation assays. These results suggest a role for PICK1 in modulating PKC.alpha.-evoked phosphorylation of mGluR7a.
REFERENCE COUNT: 35
REFERENCE(S): (1) Brakeman, P; Nature 1997, V386, P284 CAPLUS
(3) Dev, K; Neuropharmacology 1999, V38, P635 CAPLUS
(4) Dong, H; Nature 1997, V386, P279 CAPLUS
(5) Ferguson, S; Science 1996, V271, P363 CAPLUS
(6) Flor, P; Neuropharmacology 1997, V36, P153 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 37 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001060642 MEDLINE
DOCUMENT NUMBER: 20521552 PubMed ID: 11069586
TITLE: The Calliphora rpa mutant lacks the ***PDZ*** domain-assembled INAD signalling complex.
AUTHOR: Huber A; Belusic G; Da Silva N; Bahner M; Gerdon G; Draslar K; Paulsen R
CORPORATE SOURCE: Institute of Zoology, Department of Cell Biology and Neurobiology, University of Karlsruhe, Haid-und-Neu-Str. 9, D-76131 Karlsruhe, Germany.. dc05@rz.uni-karlsruhe.de
SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2000 Nov) 12 (11) 3909-18.
Journal code: BYG. ISSN: 0953-816X.
PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001129
Entered Medline: 20001222

AB The visual transduction cascade of fly photoreceptors is a G protein-coupled phospholipase C-signalling pathway which is assembled into a supramolecular signalling complex by the ***PDZ*** (postsynaptic density protein-95, discs large, ZO-1) domain protein INAD (inactivation no afterpotential D). The norpA-encoded phospholipase Cbeta, the light-activated transient receptor potential (TRP) Ca2+ channel and an eye-specific ***protein*** ***kinase*** ***C*** are bound to INAD and together form the core of the signalling complex. In the present study we show that the Calliphora rpa mutant, which has previously been hypothesized to represent an equivalent of Drosophila norpA mutants, has normal amounts of norpA mRNA but fails to express inaD mRNA. Electrophysiological recordings from the eyes of the rpa mutant reveal that the electroretinogram is reduced (about 12% of wild type) but not completely absent, and that it exhibits markedly prolonged deactivation kinetics. Furthermore, rpa mutants display a slow, light-dependent degeneration of the photoreceptor cells. With respect to the INAD signalling complex, the rpa mutant is similar to the Drosophila inaD null mutant: not only INAD itself, but also the other core components of the INAD signalling complex, are reduced or absent in photoreceptor membranes of rpa flies. Residual TRP is localized throughout the plasma membrane of the photoreceptor cell, rather than being restricted to the microvillar photoreceptor membrane. [35S]methionine-labelling of newly synthesized retinal proteins reveals that TRP is synthesized in the rpa mutant at wild-type level, but is transported to or incorporated into the microvillar photoreceptor membrane at a much lower rate. We thus suggest, that the formation of the INAD signalling complex is required for specifically targeting its components to the photoreceptor membrane.

L13 ANSWER 8 OF 37 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000112863 MEDLINE
DOCUMENT NUMBER: 20112863 PubMed ID: 10644758
TITLE: The visual G protein of fly photoreceptors interacts with the ***PDZ*** domain assembled INAD signaling complex via direct binding of activated Galpha(q) to phospholipase cbeta.
AUTHOR: Bahner M; Sander P; Paulsen R; Huber A
CORPORATE SOURCE: Department of Cell, Institute of Zoology, University of Karlsruhe, D-76128 Karlsruhe, Germany.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jan 28) 275 (4) 2901-4.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229

AB Visual transduction in the compound eye of flies is a well-established model system for the study of G protein-coupled transduction pathways. Pivotal components of this signaling pathway, including the principal light-activated Ca(2+) channel transient receptor potential, an eye-specific ***protein*** ***kinase*** ***C*** , and the norpA-encoded phospholipase Cbeta, are assembled into a supramolecular signaling complex by the modular ***PDZ*** domain protein INAD. We have used immunoprecipitation assays to study the interaction of the heterotrimeric visual G protein with this INAD signaling complex. Light-activated Galpha(q)- guanosine 5'-O-(thiotriphosphate) and AlF(4)(-)-activated Galpha(q), but not Gbetagamma, form a stable complex with the INAD signaling complex. This interaction requires the presence of norpA-encoded phospholipase Cbeta, indicating that phospholipase Cbeta is the target of activated Galpha(q). Our data establish that the INAD signaling complex is a light-activated target of the phototransduction pathway, with Galpha(q) forming a molecular on-off switch that shuttles the visual signal from activated rhodopsin to INAD-linked phospholipase Cbeta.

L13 ANSWER 9 OF 37 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000392524 MEDLINE
DOCUMENT NUMBER: 20334987 PubMed ID: 10873802
TITLE: A human homolog of the C. elegans polarity determinant Par-6 links Rac and Cdc42 to PKCzeta signaling and cell transformation.
AUTHOR: Qiu R G; Abo A; Steven Martin G
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California at Berkeley, 94720, USA.
SOURCE: CURRENT BIOLOGY, (2000 Jun 15) 10 (12) 697-707. Journal code: B44; 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000824 Last Updated on STN: 20000824 Entered Medline: 20000816

AB BACKGROUND: Rac and Cdc42 are members of the Rho family of small GTPases. They modulate cell growth and polarity, and contribute to oncogenic transformation by Ras. The molecular mechanisms underlying these functions remain elusive, however. RESULTS: We have identified a novel effector of Rac and Cdc42, hPar-6, which is the human homolog of a cell-polarity determinant in Caenorhabditis elegans. hPar-6 contains a ***PDZ*** domain and a Cdc42/Rac interactive binding (CRIB) motif, and interacts with Rac1 and Cdc42 in a GTP-dependent manner. hPar-6 also binds directly to an atypical ***protein*** ***kinase*** ***C*** isoform, PKCzeta, and forms a stable ternary complex with Rac1 or Cdc42 and PKCzeta. This association results in stimulation of PKCzeta kinase activity. Moreover, hPar-6 potentiates cell transformation by Rac1/Cdc42 and its interaction with Rac1/Cdc42 is essential for this effect. Cell transformation by hPar-6 involves a PKCzeta-dependent pathway distinct from the pathway mediated by Raf. CONCLUSIONS: These findings indicate that Rac/Cdc42 can regulate cell growth through Par-6 and PKCzeta, and suggest that deregulation of cell-polarity signaling can lead to cell transformation.

L13 ANSWER 10 OF 37 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000494612 MEDLINE
DOCUMENT NUMBER: 20394297 PubMed ID: 10934475
TITLE: A mammalian PAR-3-PAR-6 complex implicated in Cdc42/Rac1 and aPKC signalling and cell polarity.
COMMENT: Comment in: Nat Cell Biol. 2000 Aug;2(8):E143-5
AUTHOR: Lin D; Edwards A S; Fawcett J P; Mbamalu G; Scott J D; Pawson T
CORPORATE SOURCE: Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada.
CONTRACT NUMBER: DK44239 (NIDDK)
SOURCE: NATURE CELL BIOLOGY, (2000 Aug) 2 (8) 540-7. Journal code: DIQ; 100890575. ISSN: 1465-7392.
PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027 Last Updated on STN: 20001027 Entered Medline: 20001019

AB Cellular asymmetry is critical for the development of multicellular organisms. Here we show that homologues of proteins necessary for asymmetric cell division in Caenorhabditis elegans associate with each other in mammalian cells and tissues. mPAR-3 and mPAR-6 exhibit similar expression patterns and subcellular distributions in the CNS and associate through their ***PDZ*** (PSD-95/Dlg/ZO-1) domains. mPAR-6 binds to Cdc42/Rac1 GTPases, and mPAR-3 and mPAR-6 bind independently to atypical ***protein*** ***kinase*** ***C*** (aPKC) isoforms. In vitro, mPAR-3 acts as a substrate and an inhibitor of aPKC. We conclude that mPAR-3 and mPAR-6 have a scaffolding function, coordinating the activities of several signalling proteins that are implicated in mammalian cell polarity.

L13 ANSWER 11 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:114086 BIOSIS
DOCUMENT NUMBER: PREV200100114086
TITLE: Peptide binding studies of GST and 6His-cmyc tagged forms of the ***Fas*** binding ***PDZ*** domain of the protein tyrosine phosphatase FAP-1.
AUTHOR(S): Haye, H. R. (1); Blowers, D. P. (1); Hampton, I. P. (1); Taylor, I. W. (1); Grundy, C. (1); Tonge, D. W. (1)
CORPORATE SOURCE: (1) AstraZeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG UK
SOURCE: Biochemical Society Transactions, (October, 2000) Vol. 28, No. 5, pp. A429. print.
Meeting Info.: 18th International Congress of Biochemistry and Molecular Biology Birmingham, UK July 16-20, 2000
ISSN: 0300-5127.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L13 ANSWER 12 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:566600 CAPLUS
DOCUMENT NUMBER: 133:218038
TITLE: Targeting of PKA to glutamate receptors through a MAGUK-AKAP complex
AUTHOR(S): Colledge, Marcie; Dean, Rebecca A.; Scott, Gregory K.; Langeberg, Lorene K.; Huganir, Richard L.; Scott, John D.
CORPORATE SOURCE: Howard Hughes Medical Institute Vollum Institute, Oregon Health Sciences University, Portland, OR, 97201, USA
SOURCE: Neuron (2000), 27(1), 107-119
CODEN: NERNET; ISSN: 0896-6273
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Compartmentalization of glutamate receptors with the signaling enzymes that regulate their activity supports synaptic transmission. Two classes of binding proteins organize these complexes: the MAGUK proteins that cluster glutamate receptors and AKAPs that anchor kinases and phosphatases. The authors demonstrate that glutamate receptors and PKA are recruited into a macromol. signaling complex through direct interaction between the MAGUK proteins, PSD-95 and SAP97, and AKAP79/150. The SH3 and GK regions of the MAGUKs mediate binding to the AKAP. Cell-based studies indicate that phosphorylation of AMPA receptors is enhanced by a SAP97-AKAP79 complex that directs PKA to GluR1 via a ***PDZ*** domain interaction. As AMPA receptor phosphorylation is implicated in regulating synaptic plasticity, these data suggest that a MAGUK-AKAP complex may be centrally involved.
REFERENCE COUNT: 60
REFERENCE(S): (1) Anderson, J; Curr Biol 1996, V6, P382 CAPLUS
(2) Banke, T; J Neurosci 2000, V20, P89 CAPLUS
(3) Barria, A; J Biol Chem 1997, V272, P32727 CAPLUS
(5) Cho, K; Neuron 1992, V9, P929 CAPLUS
(6) Coghlan, V; Science 1995, V267, P108 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999401588 EMBASE
TITLE: Identification of a novel PSD-95/Dlg/ZO-1 (***PDZ***)-like protein interacting with the C terminus of presenilin-1.
AUTHOR: Xu X.; Shi Y.-C.; Wu X.; Gambetti P.; Sui D.; Cui M.-Z.
CORPORATE SOURCE: X. Xu, Dept. of Pathology, University of Tennessee, 2407 River Dr., Knoxville, TN 37996, United States. xmx@utk.edu
SOURCE: Journal of Biological Chemistry, (1999) 274/46 (32543-32546).
Refs: 25
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Presenilin-1 (PS-1) is the most causative Alzheimer gene product, and its function is not well understood. In an attempt to elucidate the function of PS-1, we screened a human brain cDNA library for PS-1-interacting proteins using the yeast two-hybrid system and isolated a novel protein containing a PSD-95/Dlg/ZO-1 (***PDZ***)-like domain. This novel PS-1-associated protein (PSAP) shares a significant similarity with a Caenorhabditis elegans protein of unknown function. Northern blot analysis revealed that PSAP is predominantly expressed in the brain. Deletion of the first four C-terminal amino acid residues of PS-1, which contain the ***PDZ*** domain-binding motif (Gln-Phe-Tyr- Ile), reduced the binding activity of PS-1 toward PSAP 4-fold. These data suggest that PS-1 may associate with a ***PDZ*** -like domain-containing protein in vivo and thus may participate in receptor or channel clustering and intracellular signaling events in the brain.

L13 ANSWER 14 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8
ACCESSION NUMBER: 2000149441 EMBASE
TITLE: Neuronal interleukin-16, (NIL-16): A dual function ***PDZ*** domain protein.
AUTHOR: Kurschner C.; Yuzaki M.
CORPORATE SOURCE: Dr. C. Kurschner, Dept. of Developmental Neurobiology, St. Jude Children's Res. Hospital, Memphis, TN 38105, United States
SOURCE: Journal of Neuroscience, (15 Sep 1999) 19/18 (7770-7780). Refs: 62
ISSN: 0270-6474 CODEN: JNRSDS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Interleukin (IL)-16 is a proinflammatory cytokine that has attracted widespread attention because of its ability to block HIV replication. We describe the identification and characterization of a large neuronal IL-16 precursor, NIL-16. The N-terminal half of NIL-16 constitutes a novel ***PDZ*** domain protein sequence, whereas the C terminus is identical with splenocyte- derived mouse pro-IL-16. IL-16 has been characterized only in the immune system, and the identification of NIL-16 marks a previously unsuspected connection between the immune and the nervous systems. NIL-16 is a cytosolic protein that is detected only in neurons of the cerebellum and the hippocampus. The N-terminal portion of NIL-16 interacts selectively with a variety of neuronal ion channels, which is similar to the function of many other ***PDZ*** domain proteins that serve as intracellular scaffolding proteins. Among the NIL-16-interacting proteins is the class C .alpha.1 subunit of a mouse brain calcium channel (mbC .alpha.1). The C terminus of NIL-16 can be processed by caspase-3, resulting in the release of secreted IL-16. Furthermore, in cultured cerebellar granule neurons undergoing apoptosis, NIL-16 proteolysis parallels caspase-3 activation. Cerebellar granule neurons express the IL-16 receptor ***CD4*** . Exposure of these cells to IL-16 induces expression of the immediate-early gene, c-fos, via a signaling pathway that involves tyrosine phosphorylation. This suggests that IL-16 provides an autocrine function in the brain. Therefore, we hypothesize that NIL-16 is a dual function protein in the nervous system that serves as a secreted signaling molecule as well as a scaffolding protein.

L13 ANSWER 15 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:164289 CAPLUS
DOCUMENT NUMBER: 130:306989
TITLE: Modulation of the channel activity of the .epsilon.2/.zeta.1-subtype N-methyl D-aspartate receptor by PSD-95
AUTHOR(S): Yamada, Yasue; Chochi, Yasuyo; Takamiya, Kougo; Sobue, Kenji; Inui, Makoto
CORPORATE SOURCE: Department of Pharmacology, Yamaguchi University School of Medicine, Yamaguchi, 755- 8505, Japan
SOURCE: J. Biol. Chem. (1999), 274(10), 6647-6652
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal
LANGUAGE: English
AB A channel-assocd. protein PSD-95 has been shown to induce clustering of NMDA receptors, interacting with the COOH terminus of the .epsilon. subunit of the receptors. The effects of PSD-95 on the channel activity of the .epsilon.2/.zeta.1 heteromeric NMDA receptor were examd. by injection of PSD-95 cRNA into Xenopus oocytes expressing the NMDA receptors. Expression of PSD-95 decreased the sensitivity of the NMDA receptor channels to L-glutamate. Mutational studies showed that the interaction between the COOH terminus of the .epsilon.2 subunit of the NMDA receptor and the second PSD-95/Dlg/ZO-1 domain of PSD-95 is crit. for the decrease in glutamate sensitivity. It is known that ***protein*** ***kinase*** ***C*** markedly potentiates the channel activity of the NMDA receptor expressed in oocytes. PSD-95 inhibited the ***protein*** ***kinase*** ***C*** -mediated potentiation of the channels. Thus, we demonstrated that PSD-95 functionally modulates the channel activity of the .epsilon.2/.zeta.1 NMDA receptor. PSD-95 makes signal transmission more efficient by clustering the channels at postsynaptic sites. In addn. to this, our results suggest that PSD-95 plays a protective role against neuronal excitotoxicity by decreasing the glutamate sensitivity of the channels and by inhibiting the ***protein*** ***kinase*** ***C*** -mediated potentiation of the channels.
REFERENCE COUNT: 46
REFERENCE(S): (1) Bliss, T; Nature 1993, V361, P31 CAPLUS
(2) Brenman, J; Cell 1996, V84, P757 CAPLUS
(3) Chen, L; Neuron 1991, V7, P319 CAPLUS
(4) Chen, S; J Neurochem 1996, V67, P194 CAPLUS
(5) Cho, K; Neuron 1992, V9, P929 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:637250 CAPLUS
DOCUMENT NUMBER: 131:332216
TITLE: Phosphorylation of serine-880 in GluR2 by ***protein*** ***kinase*** ***C*** prevents its C terminus from binding with glutamate receptor-interacting protein
AUTHOR(S): Matsuda, Shinji; Mikawa, Sumiko; Hirai, Hirokazu
CORPORATE SOURCE: Laboratory for Memory and Learning, RIKEN Brain Science Institute, Saitama, 351-0198, Japan
SOURCE: J. Neurochem. (1999), 73(4), 1765-1768
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphorylation of the glutamate receptor is an important mechanism of synaptic plasticity. The authors show that the C terminus of GluR2 of the .alpha.-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor is phosphorylated by ***protein*** ***kinase*** ***C*** and that serine-880 is the major phosphorylation site. This phosphorylation also occurs in human embryonic kidney (HEK) cells by addn. of 12-O-tetradecanoylphorbol 13-acetate. The authors' immunopptn. expt. revealed that the phosphorylation of serine-880 in GluR2 drastically reduced the affinity for glutamate receptor-interacting protein (GRIP), a synaptic ***PDZ*** domain-contg. protein, in vitro and in HEK cells. This result suggests that modulation of serine-880 phosphorylation in GluR2 controls the clustering of AMPA receptors at excitatory synapses and consequently contributes to synaptic plasticity.
REFERENCE COUNT: 20
REFERENCE(S): (3) Blackstone, C; J Neurosci 1994, V14, P7585 CAPLUS
(4) Dong, H; Nature 1997, V386, P279 CAPLUS
(5) Hirai, H; Proc Natl Acad Sci USA 1996, V93, P6031 CAPLUS
(6) Hollmann, M; Neuron 1994, V13, P1331 CAPLUS
(7) Ito, M; Annu Rev Neurosci 1989, V12, P85 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999087263 EMBASE
TITLE: LIM-kinasel.
AUTHOR: Stanyon C.A.; Bernard O.
CORPORATE SOURCE: O. Bernard, The Walter and Eliza Hall, Institute of Medical

Research, The Royal Melbourne Hospital, Melbourne, Vic. 3050, Australia. bernard@wehi.edu.au
SOURCE: International Journal of Biochemistry and Cell Biology, (1999) 31/3-4 (389-394).
Refs: 16
ISSN: 1357-2725 CODEN: IJBBFU
PUBLISHER IDENT.: S 1357-2725(98)00116-2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB LIM-kinase1 (LIMK1) is a serine-only protein kinase that contains LIM and ***PDZ*** protein-protein interaction domains which is highly expressed in neurons. Overexpression of LIMK1 in cultured cells results in accumulation of filamentous (F-) actin. LIMK1 phosphorylates cofilin, an actin depolymerisation factor, which is then unable to bind and depolymerise F-actin. Rac-GTP enhances phosphorylation of LIMK1 and cofilin, which leads to accumulation of F-actin, while Rac-GDP and PMA reduce these effects. LIMK1 is therefore a key component of a ***signal*** ***transduction*** network that connects extracellular stimuli to changes in cytoskeletal structure. Control of cell morphology and mobility via LIMK1 activity may provide novel approaches to cancer therapy. Copyright (C) 1999 Elsevier Science Ltd.

L13 ANSWER 18 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:156603 CAPLUS
DOCUMENT NUMBER: 130:178863
TITLE: Structural biology for PH and other domains involved in ***signal*** ***transduction***
AUTHOR(S): Koshiba, Seizo; Yokoyama, Shigeyuki
CORPORATE SOURCE: Cell. Signaling Lab., Inst. Phys. Chem. Res., Wako, 351-0198, Japan
SOURCE: Tanpakushitsu Kakusan Koso (1999), 44(4), 368-379
CODEN: TAKKAJ; ISSN: 0039-9450
PUBLISHER: Kyoritsu Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 76 refs., on the three-dimensional structure of PH (pleckstrin homol.) domain, PTB (phosphotyrosine binding) domain, and ***PDZ*** domain, and their functions in intracellular ***signal*** ***transduction*** . Interaction of PH domains with heterotrimeric G protein .beta..gamma. subunit, ***protein*** ***kinase*** ***C*** , or phospholipids is discussed on the basis of structural anal. Mechanisms for substrate recognition by PTB domains and ***PDZ*** domains are also discussed.

L13 ANSWER 19 OF 37 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000012928 MEDLINE
DOCUMENT NUMBER: 20012928 PubMed ID: 10544233
TITLE: Functional interaction of ***Fas*** -associated phosphatase-1 (FAP-1) with ***p75*** (NTR) and their effect on NF-kappaB activation.
AUTHOR: Irie S; Hachiya T; Rabizadeh S; Maruyama W; Mukai J; Li Y; Reed J C; Bredesen D E; Sato T A
CORPORATE SOURCE: Molecular Oncology Laboratory, Tsukuba Life Science Center, Institute of Physical and Chemical Research (RIKEN), Ibaraki, Japan.. irie@rtc.riken.go.jp
CONTRACT NUMBER: R01 GM055147 (NIGMS)
SOURCE: FEBS LETTERS, (1999 Oct 29) 460 (2) 191-8.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF233323
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991210
AB The common neurotrophin receptor ***p75*** (NTR), a member of the tumor necrosis factor (TNF) receptor superfamily, plays an important role in

several cellular signaling cascades, including that leading to apoptosis. FAP-1 (***Fas*** -associated phosphatase-1), which binds to the cytoplasmic tail of ***Fas*** , was originally identified as a negative regulator of ***Fas*** -mediated apoptosis. Here we have shown by co-immunoprecipitation that FAP-1 also binds to the ***p75*** (NTR) cytoplasmic domain in vivo through the interaction between the third ***PDZ*** domain of FAP-1 and C-terminal Ser-Pro-Val residues of ***p75*** (NTR). Furthermore, cells expressing a FAP-1/green fluorescent protein showed intracellular co-localization of FAP-1 and ***p75*** (NTR) at the plasma membrane. To elucidate the functional role of this physical interaction, we examined TRAF6 (TNF receptor-associated factor 6)-mediated NF-kappaB activation and tamoxifen-induced apoptosis in 293T cells expressing ***p75*** (NTR). The results revealed that TRAF6-mediated NF-kappaB activation was suppressed by ***p75*** (NTR) and that the ***p75*** (NTR)-mediated NF-kappaB suppression was reduced by FAP-1 expression. Interestingly, a mutant of the ***p75*** (NTR) intracellular domain with a single substitution of a Met for Val in its C-terminus, which cannot interact with FAP-1, displayed enhanced pro-apoptotic activity in 293T transfected cells. Thus, similar to ***Fas*** , FAP-1 may be involved in suppressing ***p75*** (NTR)-mediated pro-apoptotic signaling through its interaction with three C-terminal amino acids (tSPV). Thus, FAP-1 may regulate ***p75*** (NTR)-mediated ***signal*** ***transduction*** by physiological interaction through its third ***PDZ*** domain.

L13 ANSWER 20 OF 37 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999149546 MEDLINE
DOCUMENT NUMBER: 99149546 PubMed ID: 10027300
TITLE: Clustering of AMPA receptors by the synaptic ***PDZ*** domain-containing protein PICK1.
AUTHOR: Xia J; Zhang X; Staudinger J; Huganir R L
CORPORATE SOURCE: Department of Neuroscience, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SOURCE: NEURON, (1999 Jan) 22 (1) 179-87.
Journal code: AN8; 8809320. ISSN: 0896-6273.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990316
AB Synaptic clustering of neurotransmitter receptors is crucial for efficient ***signal*** ***transduction*** and integration in neurons. ***PDZ*** domain-containing proteins such as PSD-95/SAP90 interact with the intracellular C termini of a variety of receptors and are thought to be important in the targeting and anchoring of receptors to specific synapses. Here, we show that PICK1 (protein interacting with C kinase), a ***PDZ*** domain-containing protein, interacts with the C termini of alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors in vitro and in vivo. In neurons, PICK1 specifically colocalizes with AMPA receptors at excitatory synapses. Furthermore, PICK1 induces clustering of AMPA receptors in heterologous expression systems. These results suggest that PICK1 may play an important role in the modulation of synaptic transmission by regulating the synaptic targeting of AMPA receptors.

L13 ANSWER 21 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:370992 CAPLUS
DOCUMENT NUMBER: 131:156001
TITLE: Nitric oxide signalling in the central nervous system
AUTHOR(S): Okada, Daisuke
CORPORATE SOURCE: PRESTO, JST and Laboratory for Cellular Information Processing, Brain Science Institute, Saitama, 351-0198, Japan
SOURCE: Shinkei Kenkyu no Shinpo (1999), 43(2), 169-178
CODEN: SKNSAF; ISSN: 0001-8724
PUBLISHER: Igaku Shoin Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 51 refs. The catalytic activity of neuronal nitric oxide synthase, which resembles the cytochrome P 450-reductase complex, is

regulated by calcium-calmodulin, tetrahydrobiopterin, and ***PDZ*** domain. ***Protein*** ***kinase*** ***C*** did not phosphorylate the stabilized dimer of neuronal nitric oxide synthase in vitro, suggesting that ***protein*** ***kinase*** ***C*** -dependent phosphorylation does not regulate neuronal nitric oxide synthase activity in neurons contg. enough concns. of tetrahydrobiopterin. Thus, nitric oxide synthase activation following neuronal excitation takes place through specific interactions in a spatiotemporally restricted manner. In contrast, due to ability to diffuse across cellular membranes and to react with multiple target mols., nitric oxide has multiple functions in distributed area. Concns. of nitric oxide that reach target mols. are regulated by rate and distribution of nitric oxide synthesis, target distribution, and potency of diffusion barriers. These characteristics enable nitric oxide to play unique roles as a signalling mol. in neuronal circuits. A novel technique monitoring intracellular phosphodiesterase activity suggested that nitric oxide triggered transient increases in cyclic GMP concns. within neighboring cells. In cerebellar cortex, parallel fibers and basket cells are likely to release nitric oxide which triggers cyclic GMP prodn. within Purkinje cells. These results suggest a role of cyclic GMP in the coincidence window of long-term depression.

L13 ANSWER 22 OF 37 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 2000108166 MEDLINE
DOCUMENT NUMBER: 20108166 PubMed ID: 10643554
TITLE: The organization of INAD-signaling complexes by a multivalent ***PDZ*** domain protein in Drosophila photoreceptor cells ensures sensitivity and speed of signaling.
AUTHOR: Tsunoda S; Zuker C S
CORPORATE SOURCE: Haward Hughes Medical Institute, University of California, San Diego 92093-0649, USA. susan@flyeye.ucsd.edu or. charles@flyeye.ucsd.edu
SOURCE: CELL CALCIUM, (1999 Nov) 26 (5) 165-71. Ref: 50
Journal code: CQE; 8006226. ISSN: 0143-4160.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000223

AB Phototransduction in Drosophila has emerged as an attractive model system for studying the organization of signaling cascades in vivo. In photoreceptor neurons, the multivalent ***PDZ*** protein INAD serves as a scaffold to assemble different components of the phototransduction pathway, including the effector PLC, the light-activated ion channel TRP, and a ***protein*** ***kinase*** ***C*** involved in deactivation of the light response. INAD is required for organizing and maintaining signaling complexes in the rhabdomeres of photoreceptors. This macromolecular organization endows photoreceptors with many of their signaling properties, including high sensitivity, fast activation and deactivation kinetics, and exquisite feedback regulation by small localized changes in [Ca2+]i. Assembly of transduction components into signaling complexes is also an important cellular strategy for ensuring specificity of signaling while minimizing unwanted cross-talk. In this report, we review INAD's role as a ***signal*** ***transduction*** scaffold and its role in the assembly and localization of photoreceptor complexes.

L13 ANSWER 23 OF 37 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998316342 MEDLINE
DOCUMENT NUMBER: 98316342 PubMed ID: 9651370
TITLE: Interaction of eye ***protein*** ***kinase*** ***C*** and INAD in Drosophila. Localization of binding domains and electrophysiological characterization of a loss of association in transgenic flies.
AUTHOR: Adamski F M; Zhu M Y; Bahiraei F; Shieh B H
CORPORATE SOURCE: Department of Pharmacology and Center for Molecular Neuroscience, Vanderbilt University, Nashville, Tennessee

37232-6600, USA.
CONTRACT NUMBER: EY09743 (NEI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jul 10) 273 (28) 17713-9.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 19980817
Entered Medline: 19980806

AB Drosophila eye-specific ***protein*** ***kinase*** ***C*** (eye-PKC) is involved in light adaptation and deactivation. eye-PKC, NORPA (phospholipase Cbeta), and transient-receptor-potential (TRP) (calcium channel) are integral components of a ***signal*** ***transduction*** complex organized by INAD, a protein containing five ***PDZ*** domains. We previously demonstrated the direct association between the third ***PDZ*** domain of INAD with TRP in addition to the carboxyl-terminal half of INAD with the last three residues of NORPA. In this work, the molecular interaction between eye-PKC and INAD is defined via the yeast two-hybrid and ligand overlay assays. We show that the second ***PDZ*** domain of INAD interacts with the last three residues in the carboxyl-terminal tail of eye-PKC, Thr-Ile-Ile. The association between eye-PKC and INAD is disrupted by an amino acid substitution (Ile-700 to Asp) at the final residue of eye-PKC. In flies lacking endogenous eye-PKC (inaCp215), normal visual physiology is restored upon expression of wild-type eye-PKC, whereas the eye-PKCI700D mutant is completely inactive. Flies homozygous for inaCp209 and InaDp215, a mutation that causes a loss of the INAD-TRP association, were generated. These double mutants display a more severe response inactivation than either of the single mutants. Based on these findings, we conclude that the in vivo activity of eye-PKC depends on its association with INAD and that the sensitivity of photoreceptors is cooperatively regulated by the presence of both eye-PKC and TRP in the signaling complex.

L13 ANSWER 24 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:355298 CAPLUS
DOCUMENT NUMBER: 129:26714
TITLE: FAP-1. A protein tyrosine phosphatase that is involved in ***Fas*** -mediated apoptosis
AUTHOR(S): Yano, Hiroko; Sato, Takaaki
CORPORATE SOURCE: Coll. Physicians Surgeons, Columbia Univ., New York, 10032, USA
SOURCE: Tanpakushitsu Kakusan Koso (1998), 43(8), 1193-1199
CODEN: TAKKAJ; ISSN: 0039-9450
PUBLISHER: Kyoritsu Shuppan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 26 refs., on isolation of gene for ***Fas*** -binding protein, FAP-1 (***Fas*** -assocd. phosphatase-1), the structure of FAP-1 protein, binding specificity and physiol. function of FAP-1, clin. application of ***Fas*** /FAP-1 binding inhibitors as antitumor agents, proteins involved in the ***Fas*** signaling pathway, and proteins binding to ***PDZ*** domain of FAP-1. Possible role of FAP-1 as neg. regulator for ***Fas*** -mediated signaling pathway is also discussed.

L13 ANSWER 25 OF 37 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1998345367 MEDLINE
DOCUMENT NUMBER: 98345367 PubMed ID: 9679151
TITLE: Coordination of an array of signaling proteins through homo- and heteromeric interactions between ***PDZ*** domains and target proteins.
AUTHOR: Xu X Z; Choudhury A; Li X; Montell C
CORPORATE SOURCE: Department of Biological Chemistry and Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: EY08117 (NEI)
SOURCE: JOURNAL OF CELL BIOLOGY, (1998 Jul 27) 142 (2) 545-55.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19980828
Entered Medline: 19980819

AB The rapid activation and feedback regulation of many G protein signaling cascades raises the possibility that the critical signaling proteins may be tightly coupled. Previous studies show that the ***PDZ*** domain containing protein INAD, which functions in Drosophila vision, coordinates a signaling complex by binding directly to the light-sensitive ion channel, TRP, and to phospholipase C (PLC). The INAD signaling complex also includes rhodopsin, ***protein*** ***kinase*** ***C*** (PKC), and calmodulin, though it is not known whether these proteins bind to INAD. In the current work, we show that rhodopsin, calmodulin, and PKC associate with the signaling complex by direct binding to INAD. We also found that a second ion channel, TRPL, bound to INAD. Thus, most of the proteins involved directly in phototransduction appear to bind to INAD. Furthermore, we found that INAD formed homopolymers and the homomultimerization occurred through two ***PDZ*** domains. Thus, we propose that the INAD supramolecular complex is a higher order signaling web consisting of an extended network of INAD molecules through which a G protein-coupled cascade is tethered.

L13 ANSWER 26 OF 37 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1998218574 MEDLINE
DOCUMENT NUMBER: 98218574 PubMed ID: 9559672
TITLE: The TRP Ca2+ channel assembled in a signaling complex by the ***PDZ*** domain protein INAD is phosphorylated through the interaction with ***protein*** ***kinase*** ***C*** (ePKC).
AUTHOR: Huber A; Sander P; Bahner M; Paulsen R
CORPORATE SOURCE: Zoological Institute I, University of Karlsruhe, Germany.. DC05@rz.uni-karlsruhe.de
SOURCE: FEBS LETTERS, (1998 Mar 27) 425 (2) 317-22.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980522

AB Photoreceptors which use a phospholipase C-mediated ***signal*** ***transduction*** cascade harbor a signaling complex in which the phospholipase Cbeta (PLCbeta), the light-activated Ca2+ channel TRP, and an eye-specific ***protein*** ***kinase*** ***C*** (ePKC) are clustered by the ***PDZ*** domain protein INAD. Here we investigated the function of ePKC by cloning the Calliphora homolog of Drosophila ePKC, by precipitating the TRP signaling complex with anti-ePKC antibodies, and by performing phosphorylation assays in isolated signaling complexes and in intact photoreceptor cells. The deduced amino acid sequence of Calliphora ePKC comprises 685 amino acids (MW = 78 036) and displays 80.4% sequence identity with Drosophila ePKC. Immunoprecipitations with anti-ePKC antibodies led to the coprecipitation of PLCbeta, TRP, INAD and ePKC but not of rhodopsin. Phorbolester- and Ca2+-dependent protein phosphorylation revealed that, apart from the ***PDZ*** domain protein INAD, the Ca2+ channel TRP is a substrate of ePKC. TRP becomes phosphorylated in isolated signaling complexes. TRP phosphorylation in intact photoreceptor cells requires the presence of extracellular Ca2+ in micromolar concentrations. It is proposed that ePKC-mediated phosphorylation of TRP is part of a negative feedback loop which regulates Ca2+ influx through the TRP channel.

L13 ANSWER 27 OF 37 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:582314 CAPLUS
DOCUMENT NUMBER: 132:33386
TITLE: First annual Jorge Chevesich Memorial Lecture. A supramolecular signaling complex required for Drosophila visual transduction
AUTHOR(S): Montell, Craig
CORPORATE SOURCE: Departments of Biological Chemistry and Neuroscience,

The Johns Hopkins University School of Medicine,
Baltimore, MD, 21205, USA
SOURCE: Einstein Q. J. Biol. Med. (1998), 15(4), 198-211
CODEN: EQJMD4; ISSN: 0724-6706
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 52 refs., on the proteins required for phototransduction cascade in Drosophila melanogaster. Topics discussed included TRP, a new type of cation influx channel; TRP and TRPL interaction to form heteromultimeric channels with distinct conductances; assembly of TRP and TRPL into a supramol. signaling complex (signalplex); formation of INAD homopolymers; NINAC role in rhabdomere localization; INAD signalplex function in activation and deactivation; and TRP proteins conservation in vertebrates.
REFERENCE COUNT: 52
REFERENCE(S): (1) Acharya, J; Neuron 1997, V18, P881 CAPLUS
(2) Barbacid, M; Curr Opin Cell Biol 1995, V7, P148 CAPLUS
(3) Bloomquist, B; Cell 1988, V54, P723 CAPLUS
(4) Chevesich, J; Neuron 1997, V18, P95 CAPLUS
(6) Gillo, B; Proc Natl Acad Sci USA 1996, V93, P14146 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 28 OF 37 MEDLINE
ACCESSION NUMBER: 1998429971 MEDLINE
DOCUMENT NUMBER: 98429971 PubMed ID: 9744998
TITLE: Modulation of the plasma membrane Ca2+ pump.
AUTHOR: Penniston J T; Enyedi A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mayo Foundation, Rochester, MN 55905, USA.
CONTRACT NUMBER: GM 28835 (NIGMS)
GM 55514 (NIGMS)
SOURCE: JOURNAL OF MEMBRANE BIOLOGY, (1998 Sep 15) 165 (2) 101-9.
Ref: 59
Journal code: J4E; 0211301. ISSN: 0022-2631.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981216
AB The plasma membrane calcium pump, which ejects Ca2+ from the cell, is regulated by calmodulin. In the absence of calmodulin, the pump is relatively inactive; binding of calmodulin to a specific domain stimulates its activity. Phosphorylation of the pump with ***protein*** ***kinase*** ***C*** or A may modify this regulation. Most of the regulatory functions of the enzyme are concentrated in a region at the carboxyl terminus. This region varies substantially between different isoforms of the pump, causing substantial differences in regulatory properties. The pump shares some motifs of the carboxyl terminus with otherwise unrelated proteins: The calmodulin-binding domain is a modified IQ motif (a motif which is present in myosins) and the last 3 residues of isoform 4b are a ***PDZ*** target domain. The pump is ubiquitous, with isoforms 1 and 4 of the pump being more widely distributed than 2 and 3. In some kinds of cells isoform 1 or 4 is missing, and is replaced by another isoform.

L13 ANSWER 29 OF 37 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:384272 BIOSIS
DOCUMENT NUMBER: PREV199800384272
TITLE: ***Protein*** ***kinase*** ***C*** function in ***signal*** ***transduction*** pathways: The eye-specific ***protein*** ***kinase*** ***C*** (ePKC) assembled with the TRP calcium channel by the ***PDZ*** domain protein INAD phosphorylation TRP.
AUTHOR(S): Huber, Armin; Baehner, Monika; Sander, Philipp; Paulsen, Reinhard

L9 ANSWER 21 OF 34 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998034386 MEDLINE
DOCUMENT NUMBER: 98034386 PubMed ID: 9369453
TITLE: Interference of BAD (Bcl-xL/Bcl-2-associated death promoter)-induced apoptosis in mammalian cells by 14-3-3 isoforms and P11.
AUTHOR: Hsu S Y; Kaipia A; Zhu L; Hsueh A J
CORPORATE SOURCE: Department of Gynecology and Obstetrics, Stanford University Medical School, California 94305-5317, USA.
CONTRACT NUMBER: HD31566 (NICHD)
SOURCE: MOLECULAR ENDOCRINOLOGY, (1997 Nov) 11 (12) 1858-67.
Journal code: NGZ; 8801431. ISSN: 0888-8809.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF003523
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 20000303
Entered Medline: 19971204

AB Apoptosis and survival of diverse cell types are under hormonal control, but intracellular mechanisms regulating cell death are unclear. The Bcl-2/Ced-9 family of proteins contains conserved Bcl-2 homology regions that mediate the formation of homo- or heterodimers important for enhancing or suppressing apoptosis. Unlike most other members of the Bcl-2 family, BAD (Bcl-xL/Bcl-2 associated death promoter), a death enhancer, has no C-terminal transmembrane ***domain*** for targeting to the outer mitochondrial membrane and nuclear envelope. We hypothesized that BAD, in addition to binding Bcl-xL and Bcl-2, may ***interact*** with proteins outside the Bcl-2 family. Using the yeast two-hybrid system to search for BAD-binding proteins in an ovarian fusion cDNA library, we identified multiple cDNA clones encoding different isoforms of 14-3-3, a group of evolutionally conserved proteins essential for ***signal*** ***transduction*** and cell cycle progression. Point mutation of BAD in one (S137A), but not the other (S113A), putative binding site found in diverse 14-3-3 ***interacting*** proteins abolished the ***interaction*** between BAD and 14-3-3 without affecting ***interactions*** between BAD and Bcl-2. Because the S137A BAD mutant presumably resembles an underphosphorylated form of BAD, we used this mutant to ***screen*** for additional BAD- ***interacting*** proteins in the yeast two-hybrid system. P11, a nerve growth factor-induced neurite extension factor and member of the calcium-binding S-100 protein family, ***interacted*** strongly with the mutant BAD but less effectively with the wild type protein. In Chinese hamster ovary (CHO) cells, transient expression of wild type BAD or its mutants increased apoptotic cell death, which was blocked by cotransfection with the baculovirus-derived cysteine protease inhibitor, P35. Cotransfection with 14-3-3 suppressed apoptosis induced by wild type or the S113A mutant BAD but not by the S137A mutant incapable of binding 14-3-3. Furthermore, cotransfection with P11 attenuated the proapoptotic effect of both wild type BAD and the S137A mutant. For both 14-3-3 and P11, direct binding to BAD was also demonstrated in vitro. These results suggest that both 14-3-3 and P11 may function as BAD-binding proteins to dampen its apoptotic activity. Because the 14-3-3 family of proteins could ***interact*** with key signaling proteins including Raf-1 kinase, ***protein*** ***kinase*** ***C*** , and phosphatidyl inositol 3 kinase, whereas P11 is an early response gene induced by the neuronal survival factor, nerve growth factor, the present findings suggest that BAD plays an important role in mediating communication between different ***signal*** ***transduction*** pathways regulated by hormonal signals and the apoptotic mechanism controlled by Bcl-2 family members.

L9 ANSWER 22 OF 34 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97151148 MEDLINE
DOCUMENT NUMBER: 97151148 PubMed ID: 8995684
TITLE: ***Interaction*** of an adenovirus 14.7-kilodalton protein inhibitor of tumor necrosis factor alpha cytolysis with a new member of the GTPase superfamily of signal transducers.
AUTHOR: Li Y; Kang J; Horwitz M S
CORPORATE SOURCE: Department of Microbiology and Immunology, Albert Einstein

College of Medicine, Bronx, New York 10461, USA.
CONTRACT NUMBER: 5T32 CA09060 (NCI)
P30-CA13330 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (1997 Feb) 71 (2) 1576-82.
Journal code: KCV; 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U41654
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 20000303
Entered Medline: 19970218

AB The adenovirus (Ad) 14.7-kDa E3 protein (E3-14.7K), which can inhibit tumor necrosis factor alpha (TNF-alpha) cytolysis, was used to ***screen*** HeLa cell cDNA libraries for ***interacting*** proteins in the yeast two-hybrid system. A new member of the low-molecular-weight (LMW) GTP-binding protein family with Ras and ADP-ribosylation factor homology was discovered by this selection and has been named FIP-1 (14.7K-***interacting*** protein). FIP-1 colocalized with Ad E3-14.7K in the cytoplasm especially near the nuclear membrane and in discrete foci on or near the plasma membrane. Its ***interaction*** with E3-14.7K was dependent on the FIP-1 GTP-binding ***domain*** . The stable expression of FIP-1 antisense message partially protected the cells from TNF-alpha cytolysis. FIP-1 was associated transiently with several unknown phosphorylated cellular proteins within 15 min after treatment with TNF-alpha. FIP-1 mRNA was expressed ubiquitously but at higher levels in human skeletal muscle, heart, and brain. In addition to homology to other LMW GTP-binding proteins, FIP-1 has regions of homology to two prokaryotic metalloproteases. However, there was no homology between FIP-1 and any of the recently isolated death proteins in the TNF-alpha or ***Fas*** /APO1 cytolytic pathway and no ***interaction*** with several members of the Bcl-2 family of inhibitors of apoptosis. These data suggest that FIP-1, as a cellular target for Ad E3-14.7K, is either a new intermediate on a previously described pathway or part of a novel TNF-alpha-induced cell death pathway. FIP-1 has two consensus sequences for myristoylation which would be expected to facilitate membrane association and also has sequences for Ser/Thr as well as Tyr phosphorylation that could affect its function.

L9 ANSWER 23 OF 34 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 97400205 MEDLINE
DOCUMENT NUMBER: 97400205 PubMed ID: 9257699
TITLE: ***Interaction*** of ***Fas*** (Apo-1/CD95) with proteins implicated in the ubiquitination pathway.
AUTHOR: Becker K; Schneider P; Hofmann K; Mattmann C; Tschopp J
CORPORATE SOURCE: Institute of Biochemistry, University of Lausanne, Epalinges, Switzerland.
SOURCE: FEBS LETTERS, (1997 Jul 21) 412 (1) 102-6.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U39643; SWISSPROT-P02248
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970922
Last Updated on STN: 19970922
Entered Medline: 19970905

AB ***Fas*** (Apo-1/CD95), a receptor belonging to the tumor necrosis factor receptor family, induces apoptosis when triggered by ***Fas*** ligand. Upon its activation, the cytoplasmic ***domain*** of ***Fas*** binds several proteins which transmit the death signal. We used the yeast two-hybrid ***screen*** to isolate ***Fas*** -associated proteins. Here we report that the ubiquitin-conjugating enzyme UBC9 binds to ***Fas*** at the interface between the death ***domain*** and the membrane-proximal region of ***Fas*** . This ***interaction*** is also seen in vivo. UBC9 transiently expressed in HeLa cells bound to the co-expressed cytoplasmic segment of ***Fas*** . FAF1, a ***Fas*** -associated protein that potentiates apoptosis (Chu et al. (1996) Proc. Natl. Acad. Sci. USA 92, 11894-11898), was found to contain sequences similar to ubiquitin. These results suggest that

proteins related to the ubiquitination pathway may modulate the ***Fas*** signaling pathway.

L9 ANSWER 24 OF 34 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97067117 MEDLINE
DOCUMENT NUMBER: 97067117 PubMed ID: 8910519
TITLE: Isolation of a NCK-associated kinase, PRK2, an SH3-binding protein and potential effector of Rho protein signaling.
AUTHOR: Quilliam L A; Lambert Q T; Mickelson-Young L A; Westwick J K; Sparks A B; Kay B K; Jenkins N A; Gilbert D J; Copeland N G; Der C J
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology and the Walther Oncology Center, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA.. lawrence_quilliam@iucc.iupui.edu
CONTRACT NUMBER: CA42978 (NCI)
CA52072 (NCI)
CA63139 (NCI)
+
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Nov 15) 271 (46) 28772-6.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970107

AB The NCK adapter protein is comprised of three consecutive Src homology 3 (SH3) protein-protein ***interaction*** domains and a C-terminal SH2 ***domain*** . Although the association of NCK with activated receptor protein-tyrosine kinases, via its SH2 ***domain*** , implicates NCK as a mediator of growth factor-induced ***signal*** ***transduction*** , little is known about the pathway(s) downstream of NCK recruitment. To identify potential downstream effectors of NCK we ***screened*** a bacterial expression library to isolate proteins that bind its SH3 domains. Two molecules were isolated, the Wiskott-Aldrich syndrome protein (WASP, a putative CDC42 effector) and a serine/threonine protein kinase (PRK2, closely related to the putative Rho effector PKN). Using interspecific backcross analysis the Prk2 gene was mapped to mouse chromosome 3. Unlike WASP, which bound the SH3 domains of several signaling proteins, PRK2 specifically bound to the middle SH3 ***domain*** of NCK and (weakly) that of phospholipase Cgamma. PRK2 also specifically bound to Rho in a GTP-dependent manner and cooperated with Rho family proteins to induce transcriptional activation via the serum response factor. These data suggest that PRK2 may coordinately mediate ***signal*** ***transduction*** from activated receptor protein-tyrosine kinases and Rho and that NCK may function as an adapter to connect receptor-mediated events to Rho protein signaling.

L9 ANSWER 25 OF 34 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 96199250 MEDLINE
DOCUMENT NUMBER: 96199250 PubMed ID: 8621664
TITLE: PKN associates and phosphorylates the head-rod ***domain*** of neurofilament protein.
AUTHOR: Mukai H; Toshimori M; Shibata H; Kitagawa M; Shimakawa M; Miyahara M; Sunakawa H; Ono Y
CORPORATE SOURCE: Department of Biology, Faculty of Science, Kobe University, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Apr 19) 271 (16) 9816-22.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960627
Last Updated on STN: 19980206
Entered Medline: 19960618

AB PKN is a fatty acid-activated serine/threonine kinase that has a catalytic

domain highly homologous to that of ***protein*** ***kinase*** ***C*** in the carboxyl terminus and a unique regulatory region in the amino terminus. Recently, we reported that the small GTP-binding protein Rho binds to the amino-terminal region of PKN and activates PKN in a GTP-dependent manner, and we suggested that PKN is located on the downstream of Rho in the ***signal*** ***transduction*** pathway (Amano, M., Mukai, H., Ono, Y., Chihara, K., Matsui, T., Hamajima, Y., Okawa, K., Iwamatsu, A., and Kaibuchi, K. (1996) Science 271, 648-650; Watanabe, G., Saito, Y., Madaule, P., Ishizaki, T., Fujisawa, K., Morii, N., Mukai, H., Ono, Y. Kakizuka, A., and Narumiya, S. (1996) Science 271, 645-648). To identify other components of the PKN pathway such as substrates and regulatory proteins of PKN, the yeast two-hybrid strategy was employed. By this ***screening*** , a clone encoding the neurofilament L protein, a subunit of neuron-specific intermediate filament, was isolated. The amino-terminal regulatory region of PKN was shown to associate with the head-rod domains of other subunits of neurofilament (neurofilament proteins M and H) as well as neurofilament L protein in yeast cells. The direct binding between PKN and each subunit of neurofilament was confirmed by using the in vitro translated amino-terminal region of PKN and glutathione S-transferase fusion protein containing the head-rod ***domain*** of each subunit of neurofilament. PKN purified from rat testis phosphorylated each subunit of the native neurofilament purified from bovine spinal cord and the bacterially synthesized head-rod ***domain*** of each subunit of neurofilament. Polymerization of neurofilament L protein in vitro was inhibited by phosphorylation of neurofilament L protein by PKN. The identification and characterization of the novel ***interaction*** with PKN may contribute toward the elucidation of mechanisms regulating the function of neurofilament.

L9 ANSWER 26 OF 34 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 96335143 MEDLINE
DOCUMENT NUMBER: 96335143 PubMed ID: 8757399
TITLE: Protein-protein ***interactions*** in the yeast PKC1 pathway: Pkc1p ***interacts*** with a component of the MAP kinase cascade.
AUTHOR: Paravicini G; Friedli L
CORPORATE SOURCE: GLAXO Institue for Molecular Biology, Geneva, Switzerland.
SOURCE: MOLECULAR AND GENERAL GENETICS, (1996 Jul 26) 251 (6) 682-91.
Journal code: NGP; 0125036. ISSN: 0026-8925.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19980206
Entered Medline: 19960920

AB The two-hybrid system for the identification of protein-protein ***interactions*** was used to ***screen*** for proteins that ***interact*** in vivo with the Saccharomyces cerevisiae Pkc1 protein, a homolog of mammalian ***protein*** ***kinase*** ***C*** . Four positive clones were isolated that encoded portions of the protein kinase Mkk1, which acts downstream of Pkc1p in the PKC1-mediated signalling pathway. Subsequently, Pkc1p and the other PKC1 pathway components encoding members of a MAP kinase cascade, Bck1p (a MEKK), Mkk1p, Mkk2p (two functionally homologous MEKs), and Mpk1p (a MAP kinase), were tested pairwise for ***interaction*** in the two-hybrid assay. Pkc1p ***interacted*** specifically with small N-terminal deletions of Mkk1p, and no ***interaction*** between Pkc1p and any of the other known pathway components could be detected. ***Interaction*** between Pkc1p and Mkk1p, however, was found to be independent of Mkk1p kinase activity. Bck1p was also found to ***interact*** with Mkk1p and Mkk2p, and the ***interaction*** required only the predicted C-terminal catalytic ***domain*** of Mkk1p. Furthermore, we detected protein-protein ***interactions*** between two Bck1p molecules via their N-terminal regions. Finally, Mkk2p and Mpk1p also ***interacted*** in the two-hybrid assay. These results suggest that the members of the PKC1-mediated MAP kinase cascade form a complex in vivo and that Pkc1p is capable of directly ***interacting*** with at least one component of this pathway.

L9 ANSWER 27 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96381288 EMBASE
DOCUMENT NUMBER: 1996381288
TITLE: Looking beneath the surface: The cell death pathway of ***Fas*** /APO-1 (CD95).
AUTHOR: Stanger B.Z.
CORPORATE SOURCE: Department of Genetics, Harvard Medical School, 200 Longwood Avenue,Boston, MA 02115, United States
SOURCE: Molecular Medicine, (1996) 2/1 (7-20).
ISSN: 1076-1551 CODEN: MOMEE2
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The biochemical basis of programmed cell death is poorly understood in mammals. The cell surface receptor ***Fas*** /APO-1 (CD95) is one molecule known to be central to a number of mammalian cell death processes. Several studies in the past year have led to insights about the role of ***Fas*** /APO-1 in vivo and have also given some clues about the biochemical components of the ***Fas*** /APO-1 death pathway. This article reviews those studies and discuss models of ***Fas*** /APO-1 signaling and function. Background: Cell death occurs as a normal process in a wide variety of developmental and homeostatic contexts in metazoan organisms (1); it represents the timely and appropriate fate for many or even the majority of cells born in certain organ systems. Despite the importance and ubiquitous nature of such physiologic, or 'programmed', cell death, little is known about the molecular events that mediate this process. That a conserved biochemical pathway exists is suggested by the observation that programmed cell death is almost always accompanied by a consistent set of morphologic changes, an appearance known as apoptosis (2). The identification of the genes that control programmed cell death in higher eukaryotes has been hampered by several inherent difficulties. First, the genetic tools so useful in dissecting cell death pathways in Caenorhabditis elegans (3) and Drosophila (4) have not been available in higher eukaryotes. Second, the death-inducing properties of such genes makes genetic selection an impractical means of identification. Third, it appears that many cell death genes are constitutively expressed and present in an inactive form (5), making it unlikely that they could be discovered by techniques relying upon differential gene expressing. Finally, genes identified by virtue of an ability to induce death when overexpressed must be subjected to rigorous criteria to determine whether the cell death is of physiologic importance, since it is likely that overexpression of certain proteins may lead to toxic effects that are distinct from the in vivo roles of those proteins. Two approaches to date have yielded the most information about cell death processes: (i) identification of cell death genes by classical genetic means coupled with characterization of their mammalian homologs and (ii) ***screening*** for proteins capable of inducing cell death directly in mammalian cells. The ***Fas*** antigen/APO-1 is an example of a protein discovered using the latter approach, as it was first discovered as an inducer of cell death and later shown to be necessary and sufficient for certain programmed deaths in vivo. More recent studies have connected ***Fas*** to elements of cell death pathways in other species. It has been proposed that ***Fas*** is related to the Drosophila cell death protein Reaper, and that in signaling cell death ***Fas*** relies upon a relative of the C. elegans cell death protein CED-3. ***Fas*** may therefore represent an evolutionary conserved component of a universal cell death pathway.

L9 ANSWER 28 OF 34 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 95318185 MEDLINE
DOCUMENT NUMBER: 95318185 PubMed ID: 7541049
TITLE: Identification of heterogeneous ribonucleoprotein A1 as a novel substrate for ***protein*** ***kinase*** ***C*** zeta.
AUTHOR: Municio M M; Lozano J; Sanchez P; Moscat J; Diaz-Meco M T
CORPORATE SOURCE: Centro de Biologia Molecular Severo Ochoa, Universidad Autonoma de Madrid, Canto Blanco, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Jun 30) 270 (26) 15884-91.

Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950817
Last Updated on STN: 19970203
Entered Medline: 19950801

AB The zeta isoform of ***protein*** ***kinase*** ***C*** (zeta PKC) has been shown to be an important step in mitogenic ***signal*** ***transduction*** . Using a yeast ***interaction*** ***screen*** to search for potential novel substrates of zeta PKC, we identified the heterogeneous ribonucleoprotein A1 (hnRNPA1). This protein specifically ***interacts*** with the catalytic ***domain*** of zeta PKC but not with its regulatory region or with the full-length protein, or with a kinase-defective mutant of the zeta PKC catalytic ***domain*** . In addition, no ***interaction*** was detected with other kinases such as Raf-1 or Mos, that, like zeta PKC, are critically involved in ***signal*** ***transduction*** , or with the catalytic ***domain*** of epsilon PKC, which is the PKC isotype with the highest homology to zeta PKC. hnRNPA1 is directly phosphorylated by both recombinant and native zeta PKC, and this phosphorylation is increased when zeta PKC is immunoprecipitated from mitogen-activated fibroblasts. As an additional control, hnRNPA1 is not phosphorylated appreciably by catalytic epsilon PKC or by a mixture of highly purified classical PKC isotypes maximally activated by phosphatidylserine and Ca2+. Treatment of quiescent cell cultures with a potent mitogen such as platelet-derived growth factor promotes a significant phosphorylation of hnRNPA1 in vivo that is impaired by expression of a dominant negative mutant of zeta PKC. Furthermore, expression of a catalytically active zeta PKC mutant phosphorylates hnRNPA1 in vivo. These findings suggest that zeta PKC could be critically involved in a novel pathway that connects membrane signaling to nuclear regulatory events, at the level of RNA transport and processing. Results also shown here by using different zeta PKC mutants suggesting the control of the cytoplasmic localization of hnRNPA1 by zeta PKC. Also of potential functional relevance are the results demonstrating that the phosphorylation by zeta PKC severely impairs both hnRNPA1 RNA binding and its ability to promote strand annealing in vitro.

L9 ANSWER 29 OF 34 MEDLINE DUPLICATE 19

ACCESSION NUMBER: 96102221 MEDLINE
DOCUMENT NUMBER: 96102221 PubMed ID: 8524870
TITLE: A ***Fas*** -associated protein factor, FAF1, potentiates ***Fas*** -mediated apoptosis.
AUTHOR: Chu K; Niu X; Williams L T
CORPORATE SOURCE: Department of Medicine, University of California, San Francisco 94143, USA.
CONTRACT NUMBER: RO1 HL32898 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Dec 5) 92 (25) 11894-8.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U39643
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960219
Last Updated on STN: 19980206
Entered Medline: 19960124

AB ***Fas*** , a member of the tumor necrosis factor receptor family, can induce apoptosis when activated by ***Fas*** ligand binding or anti-***Fas*** antibody crosslinking. Genetic studies have shown that a defect in ***Fas*** -mediated apoptosis resulted in abnormal development and function of the immune system in mice. A point mutation in the cytoplasmic ***domain*** of ***Fas*** (a single base change from T to A at base 786), replacing isoleucine with asparagine, abolishes the signal transducing property of ***Fas*** . Mice homozygous for this mutant allele (lprcg/lprcg mice) develop lymphadenopathy and a lupus-like autoimmune disease. Little is known about the mechanism of ***signal*** ***transduction*** in ***Fas*** -mediated apoptosis. In this study, we used the two-hybrid ***screen*** in yeast to isolate a ***Fas***

-associated protein factor, FAF1, which specifically ***interacts*** with the cytoplasmic ***domain*** of wild-type ***Fas*** but not the lprcg-mutated ***Fas*** protein. This ***interaction*** occurs not only in yeast but also in mammalian cells. When transiently expressed in L cells, FAF1 potentiated ***Fas*** -induced apoptosis. A search of available DNA and protein sequence data banks did not reveal significant homology between FAF1 and known proteins. Therefore, FAF1 is an unusual protein that binds to the wild type but not the inactive point mutant of ***Fas*** . FAF1 potentiates ***Fas*** -induced cell killing and is a candidate signal transducing molecule in the regulation of apoptosis.

L9 ANSWER 30 OF 34 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96009602 MEDLINE
DOCUMENT NUMBER: 96009602 PubMed ID: 7565726
TITLE: Yeast RLM1 encodes a serum response factor-like protein that may function downstream of the Mpk1 (Slt2) mitogen-activated protein kinase pathway.
AUTHOR: Watanabe Y; Irie K; Matsumoto K
CORPORATE SOURCE: Department of Molecular Biology, Faculty of Science, Nagoya University, Japan.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1995 Oct) 15 (10) 5740-9. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-D63340; GENBANK-U43281
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19980206
Entered Medline: 19951025

AB The MPK1 (SLT2) gene of Saccharomyces cerevisiae encodes a mitogen-activated protein kinase that is regulated by a kinase cascade whose known elements are Pkc1 (a homolog of ***protein*** ***kinase*** ***C***), Bck1 (Slk1) (a homolog of MEK kinase), and the functionally redundant Mpk1 activators Mkk1 and Mkk2 (homologs of MEK). An activated mutation of MKK1, MKK1P386, inhibits growth when overexpressed. This growth-inhibitory effect was suppressed by the mpk1 delta mutation, suggesting that hyperactivation of the Mpk1 pathway is toxic to cells. To search for genes that ***interact*** with the Mpk1 pathway, we isolated both chromosomal mutations and dosage suppressor genes that ameliorate the growth-inhibitory effect of overexpressed Mkk1P386. One of the genes identified by the analysis of chromosomal mutations is RLM1 (resistance to lethality of MKK1P386 overexpression), which encodes a protein homologous to a conserved ***domain*** of the MADS (Mcm1, Agamous, Deficiens, and serum response factor) box family of transcription factors. Although rlm1 delta cells grow normally at any temperature, they display a caffeine-sensitive phenotype similar to that observed in mutants defective in BCK1, MKK1/MKK2, or MPK1. A gene fusion that provides Rlm1 with a transcriptional activation ***domain*** of Gal4 suppresses bck1 delta and mpk1 delta. Â ***screening*** for dosage suppressors yielded the MSG5 genes, which encode a dual-specificity protein phosphatase. Our results suggest that Rlm1 functions as a transcription factor downstream of Mpk1 that is subject to activation by the Mpk1 mitogen-activated protein kinase pathway.

L9 ANSWER 31 OF 34 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:419511 CAPLUS
DOCUMENT NUMBER: 123:28426
TITLE: Regulation of Raf-1 kinase activity by the 14-3-3 family of proteins
AUTHOR(S): Li, Shengfeng; Janosch, Petra; Tanji, Masao; Rosenfeld, Gary C.; Waymire, Jack C.; Mischak, Harald; Kolch, Walter; Sedivy, John M.
CORPORATE SOURCE: Department Molecular Biophysics Biochemistry, Yale University School Medicine, New Haven, CT, 06520, USA
SOURCE: EMBO J. (1995), 14(4), 685-96
CODEN: EMJODG; ISSN: 0261-4189
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have identified the beta (.beta.) isoform of the 14-3-3 family of proteins as an activator of the Raf-1 protein kinase. 14-3-3 Was isolated in a yeast two-hybrid ***screen*** for Raf-1 kinase ***domain***

binding proteins. Purified bovine brain 14-3-3 ***interacted*** specifically with both c-Raf-1 and the isolated Raf-1 kinase ***domain*** . Assocn. was sensitive to the activation status of Raf-1; 14-3-3 bound to unactivated Raf-1, but not Raf-1 activated by ***protein*** ***kinase*** ***C*** .alpha. or Ras and Lck. The significance of these ***interactions*** under physiol. conditions was demonstrated by co-immunopptn. of Raf-1 and 14-3-3 from exts. of quiescent, but not mitogen-stimulated, NIH 3T3 cells. 14-3-3 Was not a preferred Raf-1 substrate in vitro and did not significantly affect Raf-1 kinase activity in a purified system. However, in cell-free exts. 14-3-3 acted as a Ras-independent activator of both c-Raf-1 and the Raf-1 kinase ***domain*** . The same results were obtained in vivo using transfection assays; 14-3-3 enhanced both c-Raf-1- and NF-.kappa.B-dependent reporter genes and accelerated Raf-1 kinase ***domain*** -triggered differentiation of PC12 cells. We conclude that 14-3-3 is a latent co-activator bound to unactivated Raf-1 in quiescent cells and mediates mitogen-triggered but Ras-independent regulatory effects aimed directly at the kinase ***domain*** .

L9 ANSWER 32 OF 34 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 95146534 MEDLINE
DOCUMENT NUMBER: 95146534 PubMed ID: 7844141
TITLE: PICK1: a perinuclear binding protein and substrate for ***protein*** ***kinase*** ***C*** isolated by the yeast two-hybrid system.
AUTHOR: Staudinger J; Zhou J; Burgess R; Elledge S J; Olson E N
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Texas M.D. Anderson Cancer Center, Houston 77030.
SOURCE: JOURNAL OF CELL BIOLOGY, (1995 Feb) 128 (3) 263-71.
Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z46720
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950316
Last Updated on STN: 19950316
Entered Medline: 19950306

AB ***Protein*** ***kinase*** ***C*** (PKC) plays a central role in the control of proliferation and differentiation of a wide range of cell types by mediating the ***signal*** ***transduction*** response to hormones and growth factors. Upon activation by diacylglycerol, PKC translocates to different subcellular sites where it phosphorylates numerous proteins, most of which are unidentified. We used the yeast two-hybrid system to identify proteins that ***interact*** with activated PKC alpha. Using the catalytic region of PKC fused to the DNA binding ***domain*** of yeast GAL4 as "bait" to ***screen*** a mouse T cell cDNA library in which cDNA was fused to the GAL4 activation ***domain*** , we cloned several novel proteins that ***interact*** with C-kinase (PICKs). One of these proteins, designated PICK1, ***interacts*** specifically with the catalytic ***domain*** of PKC and is an efficient substrate for phosphorylation by PKC in vitro and in vivo. PICK1 is localized to the perinuclear region and is phosphorylated in response to PKC activation. PICK1 and other PICKs may play important roles in mediating the actions of PKC.

L9 ANSWER 33 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94304823 EMBASE
DOCUMENT NUMBER: 1994304823
TITLE: A rapid bioassay for platelet-derived growth factor .beta.-receptor tyrosine kinase function.
AUTHOR: Graminski G.F.; Lerner M.R.
CORPORATE SOURCE: Department of Internal Medicine, Boyer Center for Molecular Medicine, Yale University School of Medicine, P.O. Box 9812,New Haven, CT 06536-0812, United States
SOURCE: Bio/Technology, (1994) 12/10 (1008-1011).
ISSN: 0733-222X CODEN: BTCHDA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have extended a melanophore-based bioassay for G-protein coupled receptors to include the functional expression of the murine platelet-derived growth factor (PDGF) .beta.-receptor. The homodimeric ligand PDGF-BB induced activation of the transiently expressed receptor in melanophore cells. This led to dose dependent pigment dispersion whereas it did not induce pigment dispersion in wild type cells. The effective concentration of PDGF-BB giving half-maximal pigment dispersion (EC50) was 1 nM after 30 minutes exposure. PDGF-AA had no ability to induce pigment dispersion in melanophore cells transiently expressing the .beta.-PDGF receptor. PDGF-BB- induced pigment dispersion could be blocked by the bisindolylmaleimide Ro 31- 8220 which is an inhibitor of ***protein*** ***kinase*** ***C*** isoenzymes. Functional expression of the PDGF .beta.-receptor extends the use of the pigment translocation assay to include transmembrane signaling receptor tyrosine kinases. It opens the opportunity for the discovery of potent agonists and antagonists through massive drug ***screening*** and investigations of functional ligand-receptor ***interactions*** for single transmembrane ***domain*** receptors.

L9 ANSWER 34 OF 34 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 93272827 MEDLINE
DOCUMENT NUMBER: 93272827 PubMed ID: 7684686
TITLE: Association of CD22 with the B cell antigen receptor.
AUTHOR: Peaker C J; Neuberger M S
CORPORATE SOURCE: Medical Research Council, Laboratory of Molecular Biology, Cambridge, GB.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1993 Jun) 23 (6) 1358-63. Journal code: EN5; 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19970203
Entered Medline: 19930701

AB The antigen receptor on B lymphocytes is composed of membrane immunoglobulin sheathed by an alpha/beta heterodimer. This structure is in several respects analogous to the antigen receptor on T cells except that, in the case of the T cell but not the B cell receptor, several receptor-associated proteins have been described which may modulate the effects of antigen ***interaction*** (e.g. ***CD4*** , CD8, CD2 and CD5). To ***screen*** for specific associations with the B cell antigen receptor that might be of only low stoichiometry, we have exploited the sensitivity of in vitro kinase assays. We show that the B cell antigen receptor associates with CD22. The association is specific and stable, but Western blotting reveals it to be of low stoichiometry (0.2 to 2% of membrane immunoglobulin is CD22 associated). The CD22/antigen receptor association was demonstrated with multiple isotypes (IgM, IgD and IgG) and was evident both in Burkitt lymphoma lines and in tonsil cells. Whilst the significance of the association is unknown, it is notable that CD22 is a B cell-specific adhesion molecule which we find contains within its cytoplasmic ***domain*** a sequence bearing high homology to the "Reth motif" implicated in ***signal*** ***transduction*** . Indeed, CD22 becomes tyrosine phosphorylated less than one minute after antigen-receptor cross-linking. Thus, it is tempting to speculate that ***interactions*** involving CD22 assist in the antigen-mediated triggering of B cell activation.

=> d his

(FILE 'HOME' ENTERED AT 15:52:30 ON 02 MAY 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 15:53:58 ON 02 MAY 2001

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L1            0 S SLGI
L2       599278 S FAS OR CD4 OR P75 OR SEROTONIN OR PROTEIN KINASE C OR ADENOMA
L3       269941 S SIGNAL TRANSDUCTION
L4       454795 S DOMAIN
L5      2300288 S INTERACT?
L6         1109 S L2 AND L3 AND L4 AND L5
L7       700029 S SCREEN?
L8           78 S L6 AND L7
L9           34 DUP REM L8 (44 DUPLICATES REMOVED)
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L9 ANSWER 1 OF 34 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:244491 CAPLUS

TITLE: Cloning of ACP33 as a novel intracellular ligand of ***CD4***

AUTHOR(S): Zeitlmann, Lutz; Sirim, Pinar; Kremmer, Elisabeth; Kolanus, Waldemar

CORPORATE SOURCE: Laboratorium fur Molekulare Biologie-Genzentrum der Universitat Munchen, Munchen, D-81377, Germany

SOURCE: J. Biol. Chem. (2001), 276(12), 9123-9132
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB ***CD4*** recruitment to T cell receptor (TCR)-peptide-major histocompatibility class II complexes is required for stabilization of low affinity antigen recognition by T lymphocytes. The cytoplasmic portion of ***CD4*** is thought to amplify TCR-initiated ***signal*** ***transduction*** via its assocn. with the protein tyrosine kinase p56lck. Here we describe a novel functional determinant in the cytosolic tail of ***CD4*** that inhibits TCR-induced T cell activation. Deletion of two conserved hydrophobic amino acids from the ***CD4*** carboxyl terminus resulted in a pronounced enhancement of ***CD4*** -mediated T cell constimulation. This effect was obsd. in the presence or absence of p56lck, implying involvement of alternative cytosolic ligands of ***CD4*** . A two-hybrid ***screen*** with the intracellular portion of ***CD4*** identified a previously unknown 33-kDa protein, ACP33 (acidic cluster protein 33), as a novel intracellular binding partner of ***CD4*** . Since ***interaction*** with ACP33 is abolished by deletion of the hydrophobic ***CD4*** C-terminal amino acids mediating repression of T cell activation, we propose that ACP33 modulates the stimulatory activity of ***CD4*** . Furthermore, we demonstrate that ***interaction*** with ***CD4*** is mediated by the noncatalytic .alpha./.beta. hydrolase fold ***domain*** of ACP33. This suggests a previously unrecognized function for .alpha./.beta. hydrolase fold domains as a peptide binding module mediating protein-protein ***interactions*** .

REFERENCE COUNT: 63

REFERENCE(S): (1) Altschul, S; Nucleic Acids Res 1997, V25, P3389 CAPLUS
(3) Aravind, L; Curr Biol 1998, V8, PR111 CAPLUS
(4) Bank, I; J Exp Med 1985, V162, P1294 CAPLUS
(5) Bonnard, M; J Immunol 1999, V162, P1252 CAPLUS
(6) Bosselut, R; J Exp Med 1999, V190, P1517 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1

ACCESSION NUMBER: 2001130597 EMBASE

TITLE: Mitogen-stimulated TIS21 protein ***interacts*** with a ***protein*** - ***kinase*** - ***C*** .alpha.-binding protein rPICK1.

AUTHOR: Lin W.-J.; Chang Y.-F.; Wang W.-L.; Huang C.-Y.F.

CORPORATE SOURCE: W.-J. Lin, Inst. of Biopharmaceutical Science, National Yang-Ming University, Taipei, 112, Taiwan,Province of China. wjlin@ym.edu.tw

SOURCE: Biochemical Journal, (15 Mar 2001) 354/3 (635-643).

Refs: 33
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB TIS21 is induced transiently by PMA and a number of extracellular stimuli. Yeast two-hybrid ***screening*** has identified three TIS21 ***interacting*** clones from a rat cDNA library [Lin, Gary, Yang, Clarke and Herschman (1996) J. Biol. Chem 271, 15034-15044]. The amino acid sequence deduced from clone 5A shows 96.9% identity with the murine PICK1, a ***protein*** ***kinase*** ***C*** .alpha. (PKC.alpha.)-binding protein postulated to act as an intracellular receptor for PKC. A fusion protein of glutathione S-transferase and rPICK1 associates with the TIS21 translated in vitro, suggesting a direct physical ***interaction*** between these two proteins. TIS21 and rPICK1 are co-immunoprecipitated from NIH 3T3 cells overexpressing these two proteins. This indicates that the ***interaction*** also occurs in mammalian cells. Deletion of the PDZ ***domain*** at the N-terminus of rPICK1 abolishes its ***interaction*** with TIS21. A putative carboxylate-binding loop required for PICK1 to bind PKC.alpha. [Staudinger, Lu and Olson (1997) J. Biol. Chem 272, 32019-32024] is within this deleted region. Our results suggest a potential competition between TIS21 and PKC for binding to PICK1. We show that recombinant TIS21 is phosphorylated by PKC in vitro. The catalytic activity of PKC towards TIS21 is significantly decreased in the presence of rPICK1, whereas phosphorylation of histone by PKC is not affected, rPICK1 seems to modulate the phosphorylation of TIS21 through specific ***interactions*** between these two proteins. TIS21 might have a role in PKC-mediated extracellular ***signal*** ***transduction*** through its ***interaction*** with rPICK1.

L9 ANSWER 3 OF 34 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001089274 MEDLINE
DOCUMENT NUMBER: 20565760 PubMed ID: 11113201
TITLE: Wsc1 and Mid2 are cell surface sensors for cell wall integrity signaling that act through Rom2, a guanine nucleotide exchange factor for Rho1.
AUTHOR: Philip B; Levin D E
CORPORATE SOURCE: Department of Biochemistry & Molecular Biology, School of Public Health, The Johns Hopkins University, Baltimore, Maryland 21205, USA.. levin@welch.jhu.edu
CONTRACT NUMBER: GM48533 (NIGMS)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2001 Jan) 21 (1) 271-80. Journal code: NGY. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB Wsc1 and Mid2 are highly O-glycosylated cell surface proteins that reside in the plasma membrane of Saccharomyces cerevisiae. They have been proposed to function as mechanosensors of cell wall stress induced by wall remodeling during vegetative growth and pheromone-induced morphogenesis. These proteins are required for activation of the cell wall integrity signaling pathway that consists of the small G-protein Rho1, ***protein*** ***kinase*** ***C*** (Pkc1), and a mitogen-activated protein kinase cascade. We show here by two-hybrid experiments that the C-terminal cytoplasmic domains of Wsc1 and Mid2 ***interact*** with Rom2, a guanine nucleotide exchange factor (GEF) for Rho1. At least with regard to Wsc1, this ***interaction*** is mediated by the Rom2 N-terminal ***domain*** . This ***domain*** is distinct from the Rho1- ***interacting*** ***domain*** , suggesting that the GEF can ***interact*** simultaneously with a sensor and with Rho1. We also demonstrate that extracts from wsc1 and mid2 mutants are deficient in the ability to catalyze GTP loading of Rho1 in vitro, providing evidence that the function of the sensor-Rom2 ***interaction*** is to stimulate nucleotide exchange toward this G-protein. In a related line of investigation, we identified the PMT2 gene in a genetic ***screen***

for mutations that confer an additive cell lysis defect with a wsc1 null allele. Pmt2 is a member of a six-protein family in yeast that catalyzes the first step in O mannosylation of target proteins. We demonstrate that Mid2 is not mannosylated in a pmt2 mutant and that this modification is important for signaling by Mid2.

L9 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:161445 CAPLUS
DOCUMENT NUMBER: 132:204013
TITLE: Using mutated G protein-coupled receptors to improve their functional expression for drug ***screening*** in yeast
INVENTOR(S): Pausch, Mark Henry; Wess, Jurgen
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012705	A2	20000309	WO 1999-US20013	19990901
WO 2000012705	A3	20001005		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9957011	A1	20000321	AU 1999-57011	19990901

PRIORITY APPLN. INFO.: US 1998-98704 P 19980901
WO 1999-US20013 W 19990901

AB Mutation of G protein-coupled receptor (GPCR) is used to improve their functional expression in yeast possibly by improving the efficiency of localization of the receptor or limiting ***interaction*** with desensitizing or antagonistic mechanisms. A rat M3 muscarinic acetyllcholine receptor deletion mutant (MAR IC3.DELTA., contg. only 22 amino acids proximal to both the 5th and 6th transmembrane helixes) has been correlated with improved functional expression in mammalian cells with retention of full ability to couple the heterotrimeric G protein, Gq(G.alpha.G.gamma.). This rat M3 MAR IC3.DELTA. is a functional GPCR showing a dose-dependent growth response to the agonist carbachol when it is expressed in yeast, while the wild type MAR is not. Mutants with similar IC3 deletion in Drosophila melanogaster MAR, rat cholecystokinin CCKB receptor, rat somatostatin receptor SSTR3 and human .alpha.2A adrenergic receptor show similar results, indicating modification of internal ***domain*** may be a generalized method to improve the function of heterologous GPCRs expressed in yeast. Deletion of a C-terminal ***domain*** of the rat neurotensin NT1 receptor and replacing Caenorhabditis elegans ***serotonin*** receptor Ce 5HTR IC3 with IC3.DELTA. of rat M3 MAR show functional expression and increased agonist sensitivity in yeast. This method is useful for high-throughput drug ***screening*** for therapeutic applications. G protein coupled receptor ***signal*** ***transduction*** yeast; muscarinic receptor ***signal*** ***transduction*** yeast G protein ***interaction*** ; GPCR mammal G protein yeast ***interaction*** .

L9 ANSWER 5 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000408268 EMBASE
TITLE: DIK, a novel protein kinase that ***interacts*** with ***protein*** ***kinase*** ***C*** .delta.: Cloning, characterization, and gene analysis.
AUTHOR: Bahr C.; Rohwer A.; Stempka L.; Rincke G.; Marks F.; Gschwendt M.
CORPORATE SOURCE: M. Gschwendt, German Cancer Research Center, D-69120 Heidelberg, Germany. m.gschwendt@dkfz.de
SOURCE: Journal of Biological Chemistry, (17 Nov 2000) 275/46 (36350-36357).

Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A novel serine/threonine kinase, termed DIK, was cloned using the yeast two-hybrid system to ***screen*** a cDNA library from the human keratinocyte cell line Ha-CaT with the catalytic ***domain*** of rat ***protein*** ***kinase*** ***C*** .delta. (PKC.delta.(cat)) cDNA as bait. The predicted 784-amino acid polypeptide with a calculated molecular mass of 86 kDa contains a catalytic kinase ***domain*** and a putative regulatory ***domain*** with ankyrin-like repeats and a nuclear localization signal. Expression of DIK at the mRNA and protein level could be demonstrated in several cell lines. The dik gene is located on chromosome 21q22.3 and possesses 8 exons and 7 introns. DIK was synthesized in an in vitro transcription/translation system and expressed as recombinant protein in bacteria, HEK, COS-7, and baculovirus-infected insect cells. In the in vitro system and in cells, but not in bacteria, various post-translationally modified forms of DIK were produced. DIK was shown to exhibit protein kinase activity toward autophosphorylation and substrate phosphorylation. The ***interaction*** of PKC.delta.(cat) and PKC.delta. with DIK was confirmed by coimmunoprecipitation of the proteins from HEK cells transiently transfected with PKC.delta.(cat) or PKC.delta. and DIK expression constructs.

L9 ANSWER 6 OF 34 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000266323 MEDLINE
DOCUMENT NUMBER: 20266323 PubMed ID: 10792047
TITLE: Phosphorylation of protein kinase N by phosphoinositide-dependent protein kinase-1 mediates insulin signals to the actin cytoskeleton.
AUTHOR: Dong L Q; Landa L R; Wick M J; Zhu L; Mukai H; Ono Y; Liu F
CORPORATE SOURCE: Department of Pharmacology and Biochemistry, The University of Texas Health Science Center, San Antonio, TX 78229, USA.
CONTRACT NUMBER: DK52933 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 May 9) 97 (10) 5089-94. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000613

AB Growth factors such as insulin regulate phosphatidylinositol 3-kinase-dependent actin cytoskeleton rearrangement in many types of cells. However, the mechanism by which the insulin signal is transmitted to the actin cytoskeleton remains largely unknown. Yeast two-hybrid ***screening*** revealed that the phosphatidylinositol 3-kinase downstream effector phosphoinositide-dependent protein kinase-1 (PDK1) ***interacted*** with protein kinase N (PKN), a Rho-binding Ser/Thr protein kinase potentially implicated in a variety of cellular events, including phosphorylation of cytoskeletal components. PDK1 and PKN ***interacted*** in vitro and in intact cells, and this ***interaction*** was mediated by the kinase ***domain*** of PDK1 and the carboxyl terminus of PKN. In addition to a direct ***interaction*** , PDK1 also phosphorylated Thr(774) in the activation loop and activated PKN. Insulin treatment or ectopic expression of the wild-type PDK1 or PKN, but not protein kinase Czeta, induced actin cytoskeleton reorganization and membrane ruffling in 3T3-L1 fibroblasts and Rat1 cells that stably express the insulin receptor (Rat1-IR). However, the insulin-stimulated actin cytoskeleton reorganization in Rat1-IR cells was prevented by expression of kinase-defective PDK1 or PDK1-phosphorylation site-mutated PKN. Thus, phosphorylation by PDK1 appears to be necessary for PKN to transduce signals from the insulin receptor to the actin cytoskeleton.

L9 ANSWER 7 OF 34 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2000307855 MEDLINE

DOCUMENT NUMBER: 20307855 PubMed ID: 10848577
TITLE: Stat1 as a component of tumor necrosis factor alpha receptor 1-TRADD signaling complex to inhibit NF-kappaB activation.
AUTHOR: Wang Y; Wu T R; Cai S; Welte T; Chin Y E
CORPORATE SOURCE: Department of Pathology, Yale University School of Medicine, New Haven, CT 06510, USA.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Jul) 20 (13) 4505-12. Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000720

AB Activated tumor necrosis factor alpha (TNF-alpha) receptor 1 (TNFR1) recruits TNFR1-associated death ***domain*** protein (TRADD), which in turn triggers two opposite signaling pathways leading to caspase activation for apoptosis induction and NF-kappaB activation for antiapoptosis gene upregulation. Here we show that Stat1 is involved in the TNFR1-TRADD signaling complex, as determined by employing a novel antibody array ***screening*** method. In HeLa cells, Stat1 was associated with TNFR1 and this association was increased with TNF-alpha treatment. TNFR1 signaling factors TRADD and ***Fas*** -associated death ***domain*** protein (FADD) were also found to ***interact*** with Stat1 in a TNF-alpha-dependent process. Our in vitro recombinant protein-protein ***interaction*** studies demonstrated that Stat1 could directly ***interact*** with TNFR1 and TRADD but not with FADD. ***Interaction*** between Stat1 and receptor- ***interacting*** protein (RIP) or TNFR-associated factor 2 (TRAF2) was not detected. Examination of Stat1-deficient cells showed an apparent increase in TNF-alpha-induced TRADD-RIP and TRADD-TRAF2 complex formation, while ***interaction*** between TRADD and FADD was unaffected. As a consequence, TNF-alpha-mediated I-kappaB degradation and NF-kappaB activation were markedly enhanced in Stat1-deficient cells, whereas overexpression of Stat1 in 293T cells blocked NF-kappaB activation by TNF-alpha. Thus, Stat1 acts as a TNFR1-signaling molecule to suppress NF-kappaB activation.

L9 ANSWER 8 OF 34 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000159058 MEDLINE
DOCUMENT NUMBER: 20159058 PubMed ID: 10692483
TITLE: Modulation of dopamine D(2) receptor signaling by actin-binding protein (ABP-280).
AUTHOR: Li M; Bermak J C; Wang Z W; Zhou Q Y
CORPORATE SOURCE: Department of Pharmacology, University of California, Irvine, California, USA.
CONTRACT NUMBER: MH57889 (NIMH)
SOURCE: MOLECULAR PHARMACOLOGY, (2000 Mar) 57 (3) 446-52. Journal code: NGR; 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000410

AB Proteins that bind to G protein-coupled receptors have recently been identified as regulators of receptor anchoring and signaling. In this study, actin-binding protein 280 (ABP-280), a widely expressed cytoskeleton-associated protein that plays an important role in regulating cell morphology and motility, was found to associate with the third cytoplasmic loop of dopamine D(2) receptors. The specificity of this ***interaction*** was originally identified in a yeast two-hybrid ***screen*** and confirmed by protein binding. The functional significance of the D(2) receptor-ABP-280 association was evaluated in human melanoma cells lacking ABP-280. D(2) receptor agonists were less potent in inhibiting forskolin-stimulated cAMP production in these cells. Maximal inhibitory responses of D(2) receptor activation were also reduced. Further yeast two-hybrid experiments showed that ABP-280

association is critically dependent on the carboxyl ***domain*** of the D(2) receptor third cytoplasmic loop, where there is a potential serine phosphorylation site (S358). Serine 358 was replaced with aspartic acid to mimic the effects of receptor phosphorylation. This mutant (D(2)S358D) displayed compromised binding to ABP-280 and coupling to adenylate cyclase. PKC activation also generated D(2) receptor signaling attenuation, but only in ABP-containing cells, suggesting a PKC regulatory role in D(2)-ABP association. A mechanism for these results may be derived from a role of ABP-280 in the clustering of D(2) receptors, as determined by immunocytochemical analysis in ABP-deficient and replete cells. Our results suggest a new molecular mechanism of modulating D(2) receptor signaling by cytoskeletal protein ***interaction*** .

L9 ANSWER 9 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999401588 EMBASE
TITLE: Identification of a novel PSD-95/Dlg/ZO-1 (PDZ)-like protein ***interacting*** with the C terminus of presenilin-1.
AUTHOR: Xu X.; Shi Y.-C.; Wu X.; Gambetti P.; Sui D.; Cui M.-Z.
CORPORATE SOURCE: X. Xu, Dept. of Pathology, University of Tennessee, 2407 River Dr., Knoxville, TN 37996, United States. xmx@utk.edu
SOURCE: Journal of Biological Chemistry, (1999) 274/46 (32543-32546).
Refs: 25
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Presenilin-1 (PS-1) is the most causative Alzheimer gene product, and its function is not well understood. In an attempt to elucidate the function of PS-1, we ***screened*** a human brain cDNA library for PS-1-***interacting*** proteins using the yeast two-hybrid system and isolated a novel protein containing a PSD-95/Dlg/ZO-1 (PDZ)-like ***domain*** . This novel PS-1-associated protein (PSAP) shares a significant similarity with a Caenorhabditis elegans protein of unknown function. Northern blot analysis revealed that PSAP is predominantly expressed in the brain. Deletion of the first four C-terminal amino acid residues of PS-1, which contain the PDZ ***domain*** -binding motif (Gln-Phe-Tyr- Ile), reduced the binding activity of PS-1 toward PSAP 4-fold. These data suggest that PS-1 may associate with a PDZ-like ***domain*** -containing protein in vivo and thus may participate in receptor or channel clustering and intracellular signaling events in the brain.

L9 ANSWER 10 OF 34 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:317301 BIOSIS
DOCUMENT NUMBER: PREV199900317301
TITLE: Characterization of a novel giant scaffolding protein, CG-NAP, that anchors multiple signaling enzymes to centrosome and the Golgi apparatus.
AUTHOR(S): Takahashi, Mikiko; Shibata, Hideki; Shimakawa, Masaki; Miyamoto, Masaaki; Mukai, Hideyuki; Ono, Yoshitaka (1)
CORPORATE SOURCE: (1) Dept. of Biology, Faculty of Science, Kobe University, 1-1 Rokkodai-cho, Nada-ku, Kobe, 657-8501 Japan
SOURCE: Journal of Biological Chemistry, (June 11, 1999) Vol. 274, No. 24, pp. 17267-17274.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A novel 450-kDa coiled-coil protein, CG-NAP (centrosome and Golgi localized PKN-associated protein), was identified as a protein that ***interacted*** with the regulatory region of the protein kinase PKN, having a catalytic ***domain*** homologous to that of ***protein*** ***kinase*** ***C*** . CG-NAP contains two sets of putative RII (regulatory subunit of protein kinase A)-binding motif. Indeed, CG-NAP tightly bound to RIIalpha in HeLa cells. Furthermore, CG-NAP was coimmunoprecipitated with the catalytic subunit of protein phosphatase 2A (PP2A), when one of the B subunit of PP2A (PR130) was exogenously

expressed in COS7 cells. CG-NAP also ***interacted*** with the catalytic subunit of protein phosphatase 1 in HeLa cells. Immunofluorescence analysis of HeLa cells revealed that CG-NAP was localized to centrosome throughout the cell cycle, the midbody at telophase, and the Golgi apparatus at interphase, where a certain population of PKN and RIIalpha were found to be accumulated. These data indicate that CG-NAP serves as a novelscaffolding protein that assembles several protein kinases and phosphatases on centrosome and the Golgi apparatus, where physiological events, such as cell cycle progression and intracellular membrane traffic, may be regulated by phosphorylation state of specific protein substrates.

L9 ANSWER 11 OF 34 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:265056 CAPLUS
DOCUMENT NUMBER: 131:69052
TITLE: The ubiquitin-homology protein, DAP-1, associates with tumor necrosis factor receptor (p60) death ***domain*** and induces apoptosis
AUTHOR(S): Liou, Mei-Ling; Liou, Hsiou-Chi
CORPORATE SOURCE: Division of Immunology, Department of Medicine, Cornell University Medical College, New York, NY, 10021, USA
SOURCE: J. Biol. Chem. (1999), 274(15), 10145-10153
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The tumor necrosis factor receptor, p60 (TNF-R1), transduces death signals via the assocn. of its cytoplasmic ***domain*** with several intracellular proteins. By ***screening*** a mammalian cDNA library using the yeast two-hybrid cloning technique, the authors isolated a ubiquitin-homol. protein, DAP-1, which specifically ***interacts*** with the cytoplasmic death ***domain*** of TNF-R1. Sequence anal. reveals that DAP-1 shares striking sequence homol. with the yeast SMT3 protein that is essential for the maintenance of chromosome integrity during mitosis. DAP-1 is nearly identical to PIC1, a protein that ***interacts*** with the PML tumor suppressor implicated in acute promyelocytic leukemia, and the sentrin protein, which assocs. with the ***Fas*** death receptor. The in vivo ***interaction*** between DAP-1 and TNF-R1 was further confirmed in mammalian cells. In transient transfection assays, overexpression of DAP-1 suppresses NF-.kappa.B/Rel activity in 293T cells, a human kidney embryonic carcinoma cell line. Overexpression of either DAP-1 or sentrin causes apoptosis of TNF-sensitive L929 fibroblast cell line, as well as TNF-resistant osteosarcoma cell line, U2OS. Furthermore, the dominant neg. ***Fas*** -assocd. death ***domain*** protein (FADD) protein blocks the cell death induced by either DAP-1 or FADD. Collectively, these observations highly suggest a role for DAP-1 in mediating TNF-induced cell death signaling pathways, presumably through the recruitment of FADD death effector.
REFERENCE COUNT: 42
REFERENCE(S): (1) Adam-Klages, S; Cell 1996, V86, P937 CAPLUS
(2) Andjelic, S; Eur J Immunol 1998, V28, P570 CAPLUS
(4) Boddy, M; Oncogene 1996, V13, P971 CAPLUS
(5) Cao, Z; Nature 1996, V383, P443 CAPLUS
(6) Castellino, A; J Biol Chem 1997, V272, P5861 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999328892 EMBASE
TITLE: Association of RACK1 and PKC.beta. with the common .beta.-chain of the IL-5/IL-3/GM-CSF receptor.
AUTHOR: Geijsen N.; Spaargaren M.; Raaijmakers J.A.M.; Lammers J.-W.J.; Koenderman L.; Coffer P.J.
CORPORATE SOURCE: P.J. Coffer, Department of Pulmonary Diseases, University Hospital Utrecht, Heidelberglaan 100, 3508 GA Utrecht, Netherlands
SOURCE: Oncogene, (9 Sep 1999) 18/36 (5126-5130).
Refs: 34
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Granulocyte macrophage colony stimulating factor (GMCSF), interleukin-3 (IL-3) and interleukin-5 (IL-5 belong to a family of cytokines that regulate proliferation, differentiation and function of haematopoietic cells. Their receptor consists of a ligand specific .alpha.-chain and a signal transducing .beta.-chain (.beta.c). While, the role of phosphotyrosine residues in the .beta.c as mediators of downstream signalling cascades has been established, little is known about non-phosphotyrosine mediated events. To identify proteins ***interacting*** with .beta.c, we ***screened*** a yeast two-hybrid library with the intracellular ***domain*** of .beta.c. We found that RACK1, a molecule associating with activated PKC, PLC.gamma. and Src kinases, associated with the membrane proximal region of .beta.c in both yeast two-hybrid, immunoprecipitation and GST-pull-down assays. The association of RACK1 was constitutive, demonstrating no alteration upon cellular stimulation. Furthermore, upon stimulation of cells with IL-5 or PMA, a complex of .beta.c and PKC.beta. was found. Together, these findings suggest a novel role for RACK1 as a possible adapter molecule associating with the intracellular ***domain*** of cytokine receptors.

L9 ANSWER 13 OF 34 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:288552 CAPLUS
DOCUMENT NUMBER: 133:146642
TITLE: The ***interaction*** of myristylated peptides with the catalytic ***domain*** of ***protein*** ***kinase*** ***C***
AUTHOR(S): Zaliani, Andrea; Pinori, Massimo; Ball, Haydn L.; DiGregorio, Giuseppina; Cremonesi, Piero; Mascagni, Paolo
CORPORATE SOURCE: Italfarmaco Research Centre, Milan, 20092, Italy
SOURCE: Pept. 1998, Proc. Eur. Pept. Symp., 25th (1999), Meeting Date 1998, 432-433. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 6 refs. ***Protein*** ***kinase*** ***C*** (PKC) plays a pivotal role in several ***signal*** ***transduction*** pathways leading to cellular development, differentiation and transformation. It consists of two functional regions, the N-terminal region with a regulatory role and the C-terminal region which is catalytic. A segment of the N-terminus (sequence 19-31) is recognized by the catalytic region and acts as an inhibitory pseudosubstrate. 30 Different peptides based on the sequence of pseudosubstrate were ***screened*** for their ability to inhibit PKS. A complete account of the study has been published elsewhere.
REFERENCE COUNT: 6
REFERENCE(S): (1) Alexander, D; Biochem J 1989, V260, P893 CAPLUS
(2) Eichholtz, T; J Biol Chem 1993, V268, P1982 CAPLUS
(3) House, C; Science 1987, V238, P1726 CAPLUS
(4) O'Brian, C; Biochem Pharmacol 1990, V39, P49 CAPLUS
(5) Zaliani, A; Drug Design Discovery 1996, V13, P63 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 34 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999038205 MEDLINE
DOCUMENT NUMBER: 99038205 PubMed ID: 9819387
TITLE: Regulation of RasGRP via a phorbol ester-responsive C1 ***domain*** .
AUTHOR: Tognon C E; Kirk H E; Passmore L A; Whitehead I P; Der C J; Kay R J
CORPORATE SOURCE: Terry Fox Laboratory, British Columbia Cancer Agency, Vancouver, British Columbia, Canada V5Z 4E6.
CONTRACT NUMBER: CA42978 (NCI)

CA55008 (NCI)
CA63071 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1998 Dec) 18 (12) 6995-7008.
Journal code: NGY; 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981224

AB As part of a cDNA library ***screen*** for clones that induce transformation of NIH 3T3 fibroblasts, we have isolated a cDNA encoding the murine homolog of the guanine nucleotide exchange factor RasGRP. A point mutation predicted to prevent ***interaction*** with Ras abolished the ability of murine RasGRP (mRasGRP) to transform fibroblasts and to activate mitogen-activated protein kinases (MAP kinases). MAP kinase activation via mRasGRP was enhanced by coexpression of H-, K-, and N-Ras and was partially suppressed by coexpression of dominant negative forms of H- and K-Ras. The C terminus of mRasGRP contains a pair of EF hands and a C1 ***domain*** which is very similar to the phorbol ester- and diacylglycerol-binding C1 domains of protein kinase Cs. The EF hands could be deleted without affecting the ability of mRasGRP to transform NIH 3T3 cells. In contrast, deletion of the C1 ***domain*** or an adjacent cluster of basic amino acids eliminated the transforming activity of mRasGRP. Transformation and MAP kinase activation via mRasGRP were restored if the deleted C1 ***domain*** was replaced either by a membrane-localizing prenylation signal or by a diacylglycerol- and phorbol ester-binding C1 ***domain*** of ***protein*** ***kinase*** ***C*** . The transforming activity of mRasGRP could be regulated by phorbol ester when serum concentrations were low, and this effect of phorbol ester was dependent on the C1 ***domain*** of mRasGRP. The C1 ***domain*** could also confer phorbol myristate acetate-regulated transforming activity on a prenylation-defective mutant of K-Ras. The C1 ***domain*** mediated the translocation of mRasGRP to cell membranes in response to either phorbol ester or serum stimulation. These results suggest that the primary mechanism of activation of mRasGRP in fibroblasts is through its recruitment to diacylglycerol-enriched membranes. mRasGRP is expressed in lymphoid tissues and the brain, as well as in some lymphoid cell lines. In these cells, RasGRP has the potential to serve as a direct link between receptors which stimulate diacylglycerol-generating phospholipase Cs and the activation of Ras.

L9 ANSWER 15 OF 34 MEDLINE DUPLICATE 7

ACCESSION NUMBER: 1998386689 MEDLINE
DOCUMENT NUMBER: 98386689 PubMed ID: 9720220
TITLE: Functional ***interaction*** of Isr1, a predicted protein kinase, with the Pkc1 pathway in Saccharomyces cerevisiae.
AUTHOR: Miyahara K; Hirata D; Miyakawa T
CORPORATE SOURCE: Department of Molecular Biotechnology, Faculty of Engineering, Hiroshima University, Japan.
SOURCE: BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY, (1998 Jul) 62 (7) 1376-80.
Journal code: BDP; 9205717. ISSN: 0916-8451.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19980930

AB Staurosporine is a potent inhibitor of ***protein*** ***kinase*** ***C*** . To identify the genes that functionally ***interact*** with the Pkc1 pathway of the yeast Saccharomyces cerevisiae, we ***screened*** for the genes that cause induced staurosporine sensitivity when overexpressed from a galactose-inducible promoter. The novel gene ISR1 encodes a predicted protein kinase with the highest sequence similarity to mammalian Raf in the kinase ***domain*** . Drug sensitivity induced by ISR1 overexpression is specific to staurosporine.

Although ISR1 disruption causes no obvious phenotype, it does exacerbate the phenotypes of a temperature-sensitive allele (stt1-1) of PKC1, but not of the mpk1 and bck1 mutants of the Mpk1 MAP kinase pathway. These results suggest that Isr1 functions in an event important for growth in a manner redundant with a Mpk1-independent branch of the Pkc1 signalling pathways.

L9 ANSWER 16 OF 34 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998407731 MEDLINE
DOCUMENT NUMBER: 98407731 PubMed ID: 9737713
TITLE: BRE: a modulator of TNF-alpha action.
AUTHOR: Gu C; Castellino A; Chan J Y; Chao M V
CORPORATE SOURCE: Department of Cell Biology & Anatomy, Cornell University Medical College, New York, New York 10021, USA.
CONTRACT NUMBER: CA45670 (NCI)
SOURCE: FASEB JOURNAL, (1998 Sep) 12 (12) 1101-8.
Journal code: FAS; 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981008
Last Updated on STN: 19981008
Entered Medline: 19980929

AB A stress-responsive gene highly expressed in brain and reproductive organs (BRE) is down-regulated after UV irradiation, DNA damaging agents, or retinoic acid treatment. The human BRE gene encodes a mRNA of 1.9 kb, which gives rise to a protein of 383 amino acids with a molecular size of 44 kilodaltons. BRE is not homologous to any known gene and its function has not been defined. Here we report that BRE was identified multiple times in a yeast two-hybrid ***screen*** of a murine cerebellar cDNA library, using the juxtamembrane ***domain*** of the p55 tumor necrosis factor alpha (TNF) receptor. The ***interaction*** between the p55 receptor and BRE was verified by an in vitro biochemical assay by using recombinant fusion proteins and by co-immunoprecipitation of transfected mammalian cells. In the yeast two-hybrid assay, BRE specifically ***interacted*** with p55 TNF receptor but not with other TNF family members such as the ***Fas*** receptor, the ***p75*** TNF receptor, and ***p75*** neurotrophin receptor. Overexpression of BRE inhibited TNF-induced NFkappaB activation, indicating that the ***interaction*** of BRE protein with the cytoplasmic region of p55 TNF receptor may modulate ***signal*** ***transduction*** by TNF-alpha.

L9 ANSWER 17 OF 34 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1998421154 MEDLINE
DOCUMENT NUMBER: 98421154 PubMed ID: 9740801
TITLE: Essential requirement for caspase-8/FLICE in the initiation of the ***Fas*** -induced apoptotic cascade.
AUTHOR: Juo P; Kuo C J; Yuan J; Blenis J
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, Boston, Massachusetts 02115, USA.
SOURCE: CURRENT BIOLOGY, (1998 Sep 10) 8 (18) 1001-8.
Journal code: B44; 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981207

AB BACKGROUND: ***Fas*** (APO-1/CD95) is a member of the tumor necrosis factor receptor (TNF-R) family and induces apoptosis when crosslinked with either ***Fas*** ligand or agonistic antibody (***Fas*** antibody). The ***Fas*** - ***Fas*** ligand system has an important role in the immune system where it is involved in the downregulation of immune responses and the deletion of peripheral autoreactive T lymphocytes. The intracellular ***domain*** of ***Fas*** ***interacts*** with several proteins including FADD (MORT-1), DAXX, RIP, FAF-1, FAP-1 and Sentrin. The adaptor protein FADD can, in turn, ***interact*** with the cysteine protease caspase-8 (FLICE/MACH/Mch5). RESULTS: In a genetic ***screen*** for essential components of the

Fas -mediated apoptotic cascade, we isolated a Jurkat T lymphocyte cell line deficient in caspase-8 that was completely resistant to ***Fas*** -induced apoptosis. Complementation of this cell line with wild-type caspase-8 restored ***Fas*** -mediated apoptosis. ***Fas*** activation of multiple caspases and of the stress kinase p38 and c-Jun NH2-terminal kinase (JNK) was completely blocked in the caspase-8-deficient cell line. Furthermore, the cell line was severely deficient in cell death induced by TNF-alpha and was partially deficient in cell death induced by ultraviolet irradiation, adriamycin and etoposide. CONCLUSIONS: This study provides the first genetic evidence that caspase-8 occupies an essential and apical position in the ***Fas*** signaling pathway and suggests that caspase-8 may participate broadly in multiple apoptotic pathways.

L9 ANSWER 18 OF 34 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998437596 MEDLINE
DOCUMENT NUMBER: 98437596 PubMed ID: 9761878
TITLE: Preliminary X-ray analysis of a C2-like ***domain*** from ***protein*** ***kinase*** ***C*** -delta.
AUTHOR: Pappa H; Dekker L V; Parker P J; McDonald N Q
CORPORATE SOURCE: Imperial Cancer Research Fund, 44 Lincoln's Inn Fields, London WC2A 3PX, England.
SOURCE: ACTA CRYSTALLOGRAPHICA. SECTION D: BIOLOGICAL CRYSTALLOGRAPHY, (1998 Jul 1) 54 (Pt 4) 693-6.
Journal code: C3C; 9305878. ISSN: 0907-4449.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981214

AB C2 domains are intracellular modules of approximately 130 residues that are found in many proteins involved in membrane trafficking and ***signal*** ***transduction*** . They are known to serve a variety of roles including binding ligands such as calcium, phospholipids and inositol polyphos-phates as well as ***interacting*** with larger macromolecules. Although originally identified in the Ca2+-dependent ***protein*** ***kinase*** ***C*** isoforms (PKC), initially no C2 ***domain*** was evident within the Ca2+-independent isoenzymes. A recent study identified a divergent C2 ***domain*** in several novel, Ca2+-independent PKCs (delta, varepsilon, eta and straight theta), located at their N-termini in a region previously referred to as a variable ***domain*** zero (Vo) [Ponting & Parker (1996). Protein Sci. 5, 2375-2390]. The functional importance of this ***domain*** in the context of the novel PKCs is at present not well understood though it has been implicated in substrate recognition. The expression, crystallization and preliminary crystallographic analysis of recombinant Vo ***domain*** (residues 1-123) from PKC-delta is reported here. Crystals were obtained from incomplete factorial ***screens*** after removal of the histidine tag used to aid purification. These crystals diffracted to Bragg spacings of approximately 3 A using a rotating-anode source and to 1.9 A using synchrotron radiation. The crystals have cell parameters of a = 60.7, b = 120.9 and c = 40.7 A and systematic absences consistent with the orthorhombic space group P212121. To facilitate structure determination we have prepared, characterized and crystallized selenomethionine-substituted material.

L9 ANSWER 19 OF 34 MEDLINE
ACCESSION NUMBER: 1998189186 MEDLINE
DOCUMENT NUMBER: 98189186 PubMed ID: 9514928
TITLE: Molecular cloning and characterization of a novel ***protein*** ***kinase*** ***C*** - ***interacting*** protein with structural motifs related to RBCC family proteins.
AUTHOR: Tokunaga C; Kuroda S; Tatematsu K; Nakagawa N; Ono Y; Kikkawa U
CORPORATE SOURCE: Biosignal Research Center, Faculty of Science, Kobe University, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Mar 17) 244 (2) 353-9.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U48248
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 20000303
Entered Medline: 19980423

AB A novel ***protein*** ***kinase*** ***C*** (PKC)-***interacting*** protein was identified by the yeast two-hybrid ***screening*** using the regulatory ***domain*** of PKC beta I as a bait. The protein contained several structural motifs such as two putative coiled-coil regions, a RING-finger, a B-box, and a B-box-like motif in the order from NH2- to COOH-terminals. The molecular organization of the protein resembles the structure of the RBCC protein family proteins which usually have a RING-finger, a B-box, and a coiled-coil region. Therefore, the protein identified was designated as RBCK1 (RBCC protein ***interacting*** with PKC 1). Northern blot analysis showed that RBCK1 gene is expressed ubiquitously among rat tissues. RBCK1 protein associated with PKC beta I and PKC zeta when coexpressed in cultured mammalian cells. By the polymerase chain reaction-assisted DNA-binding site selection and the electrophoretic mobility shift assay, RBCK1 protein was shown to bind to several DNA fragments containing TGG-rich sequences. When the yeast GAL4 DNA-binding ***domain*** fused RBCK1 protein was expressed in COS-7 cells harboring the luciferase gene placed under a synthetic promoter containing GAL4-binding sites, the fusion protein showed enhanced transcriptional activity comparing with the GAL4 DNA-binding ***domain*** . These results suggest that RBCK1 protein might be a transcription factor that has a role in the signaling pathway through PKC.

L9 ANSWER 20 OF 34 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
ACCESSION NUMBER: 97103328 EMBASE
DOCUMENT NUMBER: 1997103328
TITLE: The molecular ***interaction*** of ***Fas*** and FAP-1: A tripeptide blocker of human ***Fas*** ***interaction*** with FAP-1 promotes ***Fas*** -induced apoptosis.
AUTHOR: Yanagisawa J.; Takahashi M.; Kanki H.; Yano-Yanagisawa H.; Tazunoki T.; Sawa E.; Nishitoba T.; Kamishohara M.; Kobayashi E.; Kataoka S.; Sato T.
CORPORATE SOURCE: T. Sato, Division of Molecular Oncology, College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York, NY 10032, United States.
TS174@columbia.edu
SOURCE: Journal of Biological Chemistry, (1997) 272/13 (8539-8545).
Refs: 44
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB ***Fas*** (APO-1/CD95), which is a member of the tumor necrosis factor receptor superfamily, is a cell surface receptor that induces apoptosis. A protein tyrosine phosphatase, ***Fas*** -associated phosphatase-1 (FAP-1), that was previously identified as a ***Fas*** binding protein ***interacts*** with the C-terminal 15 amino acids of the regulatory ***domain*** of the ***Fas*** receptor. To identify the minimal region of the ***Fas*** C-terminal necessary for binding to FAP-1, we employed an in vitro inhibition assay of ***Fas*** /FAP-1 binding using a series of synthetic peptides as well as a ***screen*** of random peptide libraries by the yeast two-hybrid system. The results showed that the C-terminal three amino acids (SLV) of human ***Fas*** were necessary and sufficient for its ***interaction*** with the third PDZ (GLGF) ***domain*** of FAP-1. Furthermore, the direct cytoplasmic microinjection of this tripeptide (Ac-SLV) resulted in the induction of ***Fas*** -mediated apoptosis in a colon cancer cell line that expresses both ***Fas*** and FAP-1. Since t(S/T)X(V/L/I) motifs in the C termini of several other receptors have been shown to ***interact*** with PDZ ***domain*** in signal transducing molecules, this may represent a general motif for protein- protein ***interactions*** with important biological functions.

CORPORATE SOURCE: Inst. Zool. I, Univ. Karlsruhe, 76128 Karlsruhe Germany
SOURCE: European Journal of Cell Biology, (1998) Vol. 75, No. SUPPL. 48, pp. 59.
Meeting Info.: 22nd Annual Meeting of the Deutsche Gesellschaft fuer Zellbiologie (German Society for Cell Biology) Saarbruecken, Germany March 15-19, 1998 German Society for Cell Biology
. ISSN: 0171-9335.
DOCUMENT TYPE: Conference
LANGUAGE: English

L13 ANSWER 30 OF 37 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 1998043720 MEDLINE
DOCUMENT NUMBER: 98043720 PubMed ID: 9374505
TITLE: No evidence for involvement of mouse protein-tyrosine phosphatase-BAS-like ***Fas*** -associated phosphatase-1 in ***Fas*** -mediated apoptosis.
AUTHOR: Cuppen E; Nagata S; Wieringa B; Hendriks W
CORPORATE SOURCE: Department of Cell Biology and Histology, Institute of Cellular Signaling, University of Nijmegen, P. O. Box 9101, 6500 HB Nijmegen, The Netherlands.. w.hendriks@celbi.kun.nl
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Nov 28) 272 (48) 30215-20.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971222

AB Recently, one of the ***PDZ*** domains in the cytosolic protein-tyrosine phosphatase ***Fas*** -associated phosphatase-1 (FAP-1)/protein-tyrosine phosphatase-BAS (PTP-BAS) was shown to interact with the carboxyl-terminal tS-L-V peptide of the human ***Fas*** receptor (Sato, T., Irie, S., Kitada, S., and Reed, J. C. (1995) Science 268, 411-415), suggesting a role for protein (de)phosphorylation in ***Fas*** signaling. To investigate whether this interaction is conserved in mouse, we performed yeast two-hybrid interaction experiments and transfection studies in mouse T cell lines. For the corresponding ***PDZ*** motif in the mouse homologue of FAP-1/PTP-BAS, protein-tyrosine phosphatase-BAS-like (PTP-BL), only an interaction with human but not with mouse ***Fas*** could be detected. Presence of the tS-L-V motif proper, which is unique for human ***Fas*** , rather than the structural context of its carboxyl terminus, apparently explains the initially observed binding. To test for functional conservation of any indirect involvement of PTP-BL in ***Fas*** -mediated signaling, we generated T lymphoma cell lines stably expressing mouse or human ***Fas*** receptor with and without PTP-BL. No inhibitory effect of PTP-BL was observed upon triggering apoptosis using mouse or human ***Fas*** -activating antibodies. Together with the markedly different tissue expression patterns for PTP-BL and ***Fas*** receptor, our findings suggest that protein-tyrosine phosphatase PTP-BL does not play a key role in the ***Fas*** -mediated death pathway.

L13 ANSWER 31 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97268410 EMBASE
DOCUMENT NUMBER: 1997268410
TITLE: Characterization of the interactions between ***PDZ*** domains of the protein- tyrosine phosphatase PTPL1 and the carboxyl-terminal tail of ***Fas*** .
AUTHOR: Saras J.; Engstrom U.; Gonez L.J.; Heldin C.-H.
CORPORATE SOURCE: J. Saras, Ludwig Institute for Cancer Research, Box 595, Biomedical Centre, S-751 24 Uppsala, Sweden.
jan.saras@licr.uu.s.e
SOURCE: Journal of Biological Chemistry, (1997) 272/34 (20979-20981).
Refs: 26
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
AB The intracellular protein-tyrosine phosphatase PTPL1 has five ***PDZ*** domains and one of them, ***PDZ*** 2, has previously been shown to interact with the C-terminal tail of ***Fas*** , a member of the tumor necrosis factor receptor family. Using a peptide binding assay, we show that not only ***PDZ*** 2 but also ***PDZ*** 4 of PTPL1 interacts with high affinity with peptides derived from the C terminus of ***Fas*** . The five most C-terminal amino acid residues of ***Fas*** influence the affinity of the interaction. Whereas the glutamine and isoleucine residues in the 4th and 5th positions from the C terminus affect the interaction in a negative and positive manner, respectively, the three C- terminal amino acid residues (SLV) are necessary and sufficient for a high affinity interaction to occur. Both the carboxyl group and side chain of the valine residue at the C terminus of ***Fas*** are essential, and the leucine and serine residues in the 2nd and 3rd positions, respectively, from the C terminus are important for the interactions with ***PDZ*** 2 and ***PDZ*** 4 of PTPL1.

L13 ANSWER 32 OF 37 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 1998024192 MEDLINE
DOCUMENT NUMBER: 98024192 PubMed ID: 9356510
TITLE: Association of INAD with NORPA is essential for controlled activation and deactivation of Drosophila phototransduction in vivo.
AUTHOR: Shieh B H; Zhu M Y; Lee J K; Kelly I M; Bahiraei F
CORPORATE SOURCE: Department of Pharmacology, Vanderbilt University, Nashville, TN 37232-6600, USA..
shiehb@ctrvax.vanderbilt.edu
CONTRACT NUMBER: EY09743 (NEI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Nov 11) 94 (23) 12682-7.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971216
AB Visual transduction in Drosophila is a G protein-coupled phospholipase C-mediated process that leads to depolarization via activation of the transient receptor potential (TRP) calcium channel. Inactivation-no-afterpotential D (INAD) is an adaptor protein containing ***PDZ*** domains known to interact with TRP. Immunoprecipitation studies indicate that INAD also binds to eye-specific ***protein*** ***kinase*** ***C*** and the phospholipase C, no-receptor-potential A (NORPA). By overlay assay and site-directed mutagenesis we have defined the essential elements of the NORPA-INAD association and identified three critical residues in the C-terminal tail of NORPA that are required for the interaction. These residues, Phe-Cys-Ala, constitute a novel binding motif distinct from the sequences recognized by the ***PDZ*** domain in INAD. To evaluate the functional significance of the INAD-NORPA association in vivo, we generated transgenic flies expressing a modified NORPA, NORPAC1094S, that lacks the INAD interaction. The transgenic animals display a unique electroretinogram phenotype characterized by slow activation and prolonged deactivation. Double mutant analysis suggests a possible inaccessibility of eye-specific ***protein*** ***kinase*** ***C*** to NORPAC1094S, undermining the observed defective deactivation, and that delayed activation may similarly result from NORPAC1094S being unable to localize in close proximity to the TRP channel. We conclude that INAD acts as a scaffold protein that facilitates NORPA-TRP interactions required for gating of the TRP channel in photoreceptor cells.

L13 ANSWER 33 OF 37 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 17
ACCESSION NUMBER: 97103328 EMBASE
DOCUMENT NUMBER: 1997103328
TITLE: The molecular interaction of ***Fas*** and FAP-1: A tripeptide blocker of human ***Fas*** interaction with FAP-1 promotes ***Fas*** -induced apoptosis.
AUTHOR: Yanagisawa J.; Takahashi M.; Kanki H.; Yano-Yanagisawa H.; Tazunoki T.; Sawa E.; Nishitoba T.; Kamishohara M.;

Kobayashi E.; Kataoka S.; Sato T.
CORPORATE SOURCE: T. Sato, Division of Molecular Oncology, College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York, NY 10032, United States. TS174@columbia.edu
SOURCE: Journal of Biological Chemistry, (1997) 272/13 (8539-8545). Refs: 44
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Fas*** (APO-1/CD95), which is a member of the tumor necrosis factor receptor superfamily, is a cell surface receptor that induces apoptosis. A protein tyrosine phosphatase, ***Fas*** -associated phosphatase-1 (FAP-1), that was previously identified as a ***Fas*** binding protein interacts with the C-terminal 15 amino acids of the regulatory domain of the ***Fas*** receptor. To identify the minimal region of the ***Fas*** C-terminal necessary for binding to FAP-1, we employed an in vitro inhibition assay of ***Fas*** /FAP-1 binding using a series of synthetic peptides as well as a screen of random peptide libraries by the yeast two-hybrid system. The results showed that the C-terminal three amino acids (SLV) of human ***Fas*** were necessary and sufficient for its interaction with the third ***PDZ*** (***GLGF***) domain of FAP-1. Furthermore, the direct cytoplasmic microinjection of this tripeptide (Ac-SLV) resulted in the induction of ***Fas*** -mediated apoptosis in a colon cancer cell line that expresses both ***Fas*** and FAP-1. Since t(S/T)X(V/L/I) motifs in the C termini of several other receptors have been shown to interact with ***PDZ*** domain in signal transducing molecules, this may represent a general motif for protein-protein interactions with important biological functions.

L13 ANSWER 34 OF 37 MEDLINE
ACCESSION NUMBER: 1998044304 MEDLINE
DOCUMENT NUMBER: 98044304 PubMed ID: 9382826
TITLE: ***PDZ*** domain proteins: scaffolds for signaling complexes.
AUTHOR: Ranganathan R; Ross E M
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Pharmacology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9041, USA.. rama@chop.swmed.edu
SOURCE: CURRENT BIOLOGY, (1997 Dec 1) 7 (12) R770-3. Ref: 26
Journal code: B44; 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 20000303
Entered Medline: 19980219
AB InaD, a Drosophila photoreceptor scaffolding protein, assembles multiple signal-transducing proteins at the membrane via its five ***PDZ*** domains, enhancing speed and efficiency of vision. Extensive conservation of ***PDZ*** domains suggests that these motifs have a general role in organizing diverse signaling complexes.

L13 ANSWER 35 OF 37 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 1998016248 MEDLINE
DOCUMENT NUMBER: 98016248 PubMed ID: 9351965
TITLE: New light on TRP and TRPL.
AUTHOR: Montell C
CORPORATE SOURCE: Department of Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SOURCE: MOLECULAR PHARMACOLOGY, (1997 Nov) 52 (5) 755-63. Ref: 84
Journal code: NGR; 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971124

AB Store-operated Ca2+ entry, a mode of Ca2+ influx activated by depletion of Ca2+ from the internal stores, has been detected in a wide variety of cell types and may be the primary mechanism for Ca2+ entry in nonexcitable cells. Nevertheless, until recently, no candidate store-operated channel (SOC) had been identified molecularly. Through the serendipity of Drosophila genetics, a candidate SOC, referred to as Transient Receptor Potential (TRP), has been identified that is essential for the light-induced cation conductance in photoreceptor cells. A combination of in vitro and in vivo studies has provided strong evidence that TRP is a bona fide SOC. Moreover, TRP forms a supramolecular complex, proposed to be critical for feedback regulation and/or activation, that includes rhodopsin, phospholipase C, ***protein*** ***kinase*** ***C*** , calmodulin, and the ***PDZ*** domain-containing protein, INAD. INAD seems to be a scaffolding protein that links TRP with several of these other proteins in the complex. TRP also complexes with a related channel subunit, TRP-like, to form a heteromultimer with conductance characteristics distinct from those of TRP or TRP-like homomultimers. A family of proteins related to TRP is conserved from Caenorhabditis elegans to humans, and recent evidence indicates that at least some of these proteins are SOCs. The human TRP-related proteins may mediate many of the store-operated conductances that have been identified previously in a plethora of human cells.

L13 ANSWER 36 OF 37 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 97373949 MEDLINE
DOCUMENT NUMBER: 97373949 PubMed ID: 9230432
TITLE: A multivalent ***PDZ*** -domain protein assembles signalling complexes in a G-protein-coupled cascade.
AUTHOR: Tsunoda S; Sierralta J; Sun Y; Bodner R; Suzuki E; Becker A; Socolich M; Zuker C S
CORPORATE SOURCE: Howard Hughes Medical Institute, and Department of Biology, University of California at San Diego, La Jolla 92093-0649, USA.
SOURCE: NATURE, (1997 Jul 17) 388 (6639) 243-9.
Journal code: NSC; 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 20000303
Entered Medline: 19970807

AB How are signalling molecules organized into different pathways within the same cell? In Drosophila, the inaD gene encodes a protein consisting of five ***PDZ*** domains which serves as a scaffold to assemble different components of the phototransduction cascade, including the principal light-activated ion channels, the effector phospholipase C-beta and ***protein*** ***kinase*** ***C*** . Null inaD mutants have a dramatically reorganized subcellular distribution of signalling molecules, and a total loss of transduction complexes. Also, mutants defective in a single ***PDZ*** domain produce signalling complexes that lack the target protein and display corresponding defects in their physiology. A picture emerges of a highly organized unit of signalling, a 'transduclisome', with ***PDZ*** domains functioning as key elements in the organization of transduction complexes in vivo.

L13 ANSWER 37 OF 37 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 97157494 MEDLINE
DOCUMENT NUMBER: 97157494 PubMed ID: 9003779
TITLE: The transient receptor potential protein (Trp), a putative store-operated Ca2+ channel essential for phosphoinositide-mediated photoreception, forms a signaling complex with NorpA, InaC and InaD.
AUTHOR: Huber A; Sander P; Gobert A; Bahner M; Hermann R; Paulsen R

CORPORATE SOURCE: Zoological Institute I, University of Karlsruhe, Germany.
SOURCE: EMBO JOURNAL, (1996 Dec 16) 15 (24) 7036-45.
Journal code: EMB; 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z80230
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970227
Last Updated on STN: 19980206
Entered Medline: 19970213

AB The transient receptor potential protein (Trp) is a putative capacitative Ca2+ entry channel present in fly photoreceptors, which use the inositol 1,4,5-trisphosphate (InsP3) signaling pathway for phototransduction. By immunoprecipitation studies, we find that Trp is associated into a multiprotein complex with the norpA-encoded phospholipase C, an eye-specific ***protein*** ***kinase*** ***C*** (InaC) and with the InaD protein (InaD). InaD is a putative substrate of InaC and contains two ***PDZ*** repeats, putative protein-protein interaction domains. These proteins are present in the photoreceptor membrane at about equimolar ratios. The Trp homolog analyzed here is isolated together with NorpA, InaC and InaD from blowfly (Calliphora) photoreceptors. Compared to Drosophila Trp, the Calliphora Trp homolog displays 77% amino acid identity. The highest sequence conservation is found in the region that contains the putative transmembrane domains S1-S6 (91% amino acid identity). As investigated by immunogold labeling with specific antibodies directed against Trp and InaD, the Trp signaling complex is located in the microvillar membranes of the photoreceptor cells. The spatial distribution of the signaling complex argues against a direct conformational coupling of Trp to an InsP3 receptor supposed to be present in the membrane of internal photoreceptor Ca2+ stores. It is suggested that the organization of signal transducing proteins into a multiprotein complex provides the structural basis for an efficient and fast activation and regulation of Ca2+ entry through the Trp channel.